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The Rôle of Specific Carbohydrates in Pneumococcus Infection and Immunity*†

By OSWALD T. AVERY, M D, *New York City*

MR President; Fellows of the American College of Physicians:

I count it a great privilege to be able on this occasion to express personally my deep sense of appreciation of the distinguished honor conferred upon me by the American College of Physicians. In awarding me the John Phillips Memorial Prize I feel that you have been far too generous in your appraisal of my share in the work for which this distinction is granted. I am conscious that whatever merit may accrue to the studies in which it has been my privilege to participate is due in great part to the happy auspices under which the work is carried on, and in large measure to the devoted and hearty cooperation of my associates. To them, I am indebted for an association that to me has been a source of genuine pleasure and great helpfulness, and to them I am happy on this occasion to acknowledge my obligation.

*From the Hospital of the Rockefeller Institute, New York City

†Delivered at the San Francisco Meeting of the American College of Physicians, April 6, 1932, at the presentation of the John Phillips Memorial Prize

I find great satisfaction in the thought that in making this award, you are symbolizing in a far larger sense than the mere personal recognition implies, your faith in the spirit of research and the principles of practice expressed by Osler in these words: "To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions. To carefully observe the phenomena of life in all its phases normal and perverted, to make perfect the most difficult of all the arts, the art of observation, to call to aid the science of experimentation, to cultivate the reasoning faculty, so as to be able to know the true from the false—these are our methods. To prevent disease, to relieve suffering and to heal the sick—this is our work."

To all who cherish these ambitions, cultivate these methods, and delight in this work, the example of him in whose memory this award has been established will remain a continuing source of inspiration.

Permit me once more to assure you

of my grateful appreciation of the signal honor of being enrolled as one of the recipients of the John Phillips Memorial Prize

AN important advance in the study of infectious diseases came with the knowledge that bacteria, though simple in form and structure, exhibit differences in biological specificity as sharply defined as are those characteristic of the more complex forms of life. The study of the immunological specificity of microorganisms is not only necessary in the elucidation of the biological relationships existing between varieties of the same species of bacterium but is essential to the working out of epidemiological problems and to the development of methods useful in the control of infectious diseases by specific therapeutic and prophylactic measures.

Leaving out of consideration the promising but difficult field of chemotherapy, the problems of specific cure and prevention of infection lie in the attempt to interpret and imitate by artificial procedures certain protective processes of nature which constitute that which we call immunity. In order to imitate successfully the natural processes involved in spontaneous recovery from disease, it is necessary to know the nature of the specific reactions between the infecting agent and the body tissues of the host. The specificity of these biological processes is advantageously studied by means of the so-called immunity reactions. These serve as a measure of the capacity of the animal organism to produce protective substances, and they afford a means of studying the interaction be-

tween these specific antibodies and the infectious microorganism when both are brought together in the animal body or in the test tube.

Investigations on the specificity of these reactions have added much to our knowledge of the many and diverse problems of infection. The study, however, is one of varying complexity, the methods suitable in one instance fail utterly when applied to another type of infection. While the mechanism of the interaction between host and parasite has to a certain extent been exposed through the brilliant discoveries of Metchnikoff, Ehrlich, Behring, Bordet and others, the immediate problem lies in reconstructing for each microbe a more precise knowledge of the biological properties peculiar to it and the specific reactions which the body develops against it. One approach to this problem is the attempt to relate specific differences in biological behavior to fundamental differences in the function and chemical composition of the component parts of the bacterial cell and to determine the character of the tissue responses to these separate constituents. The total immune response of the host comprises not alone a reaction to the parasite as a whole, but, in addition, the specific and individualized responses to the chemically distinct and immunologically specific bacterial constituents.

For the past several years under the direction of Dr. Rufus Cole a number of us on the staff of the Hospital of the Rockefeller Institute have been seeking to acquire a more intimate knowledge of the relation between the immuno-chemistry and the biological activities of pneumococcus, the most

frequent and one of the most fatal of the microbic incitants of pneumonia in man

On this occasion I shall review briefly one phase of the studies, namely, the rôle of specific carbohydrates in pneumococcus infection and immunity. Because of the limited time at my disposal, I shall of necessity be obliged to omit reference to the valuable contributions of that large group of other investigators who, both in this country and abroad, have added so much to our knowledge of the problems of pneumococcus pneumonia.

You are already familiar with the renewed impetus that was given to the study of pneumonia by the working out of the biological classification of pneumococci which made possible the recognition of sharply defined and specific types within this previously confused species of microorganisms. You will recall that by the application of this method it has been possible to determine the frequency of occurrence of these specific types in pneumonia, and to recognize differences in the severity and mortality of the infections they produce, that a study of the presence of pneumococci in the mouth secretion of healthy individuals proved the dissemination of the disease-producing types by healthy carriers and convalescents and suggested a new interpretation of the epidemiology of the disease, and finally that the knowledge of type-specificity among pneumococci provides the only rational basis for the possible development of specific therapy by immune serum, which in the treatment of type I infections, at least, has proved of distinct value.

Pneumococcus is a unicellular micro-

organism which under well-defined conditions of growth is surrounded by an envelope of material known as the cell capsule. This capsular layer is particularly well developed in the case of pneumococci capable of growing and multiplying in the animal body. During growth these encapsulated cells elaborate in the medium of their environment a diffusible substance which in soluble form retains the type-specificity of the bacterial cells from which it is derived. This soluble specific substance is found not only in the filtrates of young cultures but also in the body fluids of animals experimentally infected, and in the blood and urine of patients during the course of pneumococcus pneumonia. The function of elaborating this specific material is most highly developed in the most virulent organisms. There are grounds for the belief that the capsule of these virulent cells is composed largely of this soluble specific substance. Thus, there is disposed peripherally about the cell an outer layer of capsular substance which reacts specifically with the serum of immune animals. The reaction is remarkably specific, occurring only when the anti-serum and the reacting substance are both of the same specific type. These immunological reactions form the basis of the original classification and were worked out before there was any knowledge of the chemical nature of the substances upon which type-specificity depends. The actual isolation of these specific substances in purified form, the determination of their chemical constitution and their relationship to the immunological properties of the

cell as a whole are problems to which I shall direct attention.

The type-specific capsular substances of pneumococcus, first chemically isolated by Dr. Heidelberger, have been found in each instance to belong to the class of sugar-like substances, namely, the carbohydrates. No matter from what type of pneumococcus these specific substances are recovered they all possess in common the chemical properties of complex sugars—the polysaccharides. But, interestingly enough, the capsular polysaccharide derived from each specific type of organism is chemically distinct, each possessing unique chemical properties which serve to differentiate it sharply from the others. Moreover, solutions of these capsular polysaccharides in chemically purified form, exhibit immunologically the same specificity as do the bacteria of which they originally formed a part. Some idea of how remarkably reactive these sugars are may be judged from the fact that, by the use of an appropriate serum, their presence may be detected in dilutions as high as 1:5,000,000.

Dr. Heidelberger and Dr. Goebel, studying the chemistry of the capsular polysaccharides, have shown that these substances are unusual compounds of simple sugars and uronic acids. Although possessing many properties in common, they exhibit characteristic differences in the degree to which they rotate the plane of polarized light and in their acid equivalent number. For example, of the specific substances of the first three types of pneumococcus, the type I polysaccharide differs sharply from the other two in containing nitrogen as an integral part of the

molecule, and in possessing basic as well as acidic properties; on the other hand the type II polysaccharide is a dextrorotatory weak acid and the type III a levorotatory strong acid, neither of which contains any nitrogen in the molecule. The fact that the particular constituent determining type-specificity is chemically a carbohydrate is the more striking since immunity reactions have hitherto been considered exclusively the function of proteins. Of equal importance is the fact that this selective specificity is in each instance determined by the chemical constitution of the particular polysaccharide in the capsule and that the presence of this morphological structure conditions both the invasiveness of the parasite and the immune response of the host.

The fact that polysaccharides elaborated by bacteria growing in the focus of disease may be found in the blood and urine, unchanged in specificity, indicates that the body possesses no enzymes capable of breaking them down into simpler sugars. There is no evidence that these complex bacterial sugars *as such* are directly responsible for the intoxication accompanying the infection. So far as known they are not primarily toxic, at least not in the sense of true bacterial toxins. There are facts, however, which indicate that indirectly at least they may have a harmful effect upon the natural processes of recovery. Because of their specific capacity to bind antibodies, they tend to neutralize the immune substances in the blood and thus prevent the protective antibodies from reaching the infected areas. Moreover, the capsular polysaccharides are known to exert an inhibiting action on phagocytosis, one

of the most important cellular defenses of the body against pneumococcus infection

Theoretically, at least, there is no apparent reason why these complex sugars as isolated substances should not by themselves be capable of stimulating the formation of antibodies in the animal body. Assuming that they are of sufficient molecular size, they possess in complexity of structure and colloidal behavior certain properties generally considered essential to the antigenicity of proteins. Indeed, Francis and Tillett have found that in the present state of purity the capsular polysaccharides are capable of inciting antibody production when injected in minute amounts into the skin of convalescents and normal individuals. However, with few exceptions all attempts to evoke any immune response in animals with the highly purified polysaccharides alone have been uniformly unsuccessful. On the other hand, the more these carbohydrates are chemically purified, the more reactive they become in the specific serum of immune animals. Under these conditions it appears that, removed from the bacterial cells, the capsular polysaccharides still retain unimpaired the property of binding with antibodies, although in this form they become quantitatively less active in stimulating antibody production in animals. In this respect they may rightly be included in the group of immunologically important substances which Landsteiner has called haptens,—substances which have lost more or less completely their antibody-stimulating function without impairment of the property of specifically combining with antibodies.

The elaboration of the capsular polysaccharide is an important function of the cell. When this function is suppressed or inhibited, as it may be under certain experimental conditions of growth, the capsule is no longer formed. As a result the organisms lose their type-specificity and exhibit only the common, undifferentiated characters of the species. On the basis of colony differentiation these degraded organisms are spoken of as the "R" or rough forms, and the original encapsulated types are referred to as the smooth or "S" organisms. The unencapsulated R forms of pneumococci, irrespective of their type derivation, are no longer capable of invading the animal body; they have lost their virulence, and are readily taken up and destroyed by the phagocytes of the host; immunologically they exhibit only the species-specificity common to all the degraded R forms of pneumococcus. This transformation resulting in a loss of specific characters may occur in the animal body as well as in the test tube. However, these degraded, avirulent variants do not necessarily remain the harmless saprophytes they were originally thought to be, since it is now known that under suitable conditions they may regain all the specific characteristics that distinguished the original parasitic type from which they came.

Of even greater biological interest is the phenomenon of the inter-convertibility of the specific types of pneumococcus. Griffith of London first showed experimentally by a special technic in mice that R forms derived from one specific type of pneumococcus may be caused to acquire the characteristics of

another specific type. This important fact has been confirmed by a number of investigators. In addition, Dawson and Sia by special cultural methods, have found that the actual change from one specific type of pneumococcus to another may be brought about in the test tube outside the animal body.

The experimental evidence now available seems to indicate that any R strain of pneumococcus has potentially the function of elaborating any one of the specific capsular polysaccharides;—the particular one being determined by a particular stimulus of a specific nature. Aloway has recently found that this potential function latent in the living R cells may be specifically activated by the addition to an appropriate medium of a bacterial extract prepared from a given specific type of pneumococcus. Under these conditions, the R forms irrespective of their type derivation again elaborate a capsular material identical in specificity with that of the type of pneumococcus from which the extract was prepared.

There is at present no certain proof that transformations of this kind ever occur spontaneously in nature. Nor is there as yet any epidemiological or clinical evidence that this form of reversible adaption is a factor in the origin of human infection. However, the experimental evidence leaves no doubt that the non-invasive, non-encapsulated R cells under favorable circumstances are potentially capable of again developing into highly virulent organisms and that the acquisition of virulence is invariably associated with the restoration of the function of elaborating the specific capsular carbo-

hydrates. Indeed, it is most significant that no matter whether one considers pneumococcus from the viewpoint of virulence, antigenicity, or its capacity to undergo variation, the single determining factor associated with all these characters is the function of synthesizing the specific capsular polysaccharides. Scarcely less important is the fact that the immunological specificity of each of the specific types of pneumococcus depends upon the chemical individuality of the particular carbohydrate in the cell capsule.

As chemical substances, separate and apart from the bacterial cells, these carbohydrates have been found to incite specific reactions in the tissues of sensitized animals and in the skin of patients convalescent from pneumococcus pneumonia. Guinea pigs passively sensitized with the precipitating serum of an immune rabbit suffer violent anaphylactic shock and die within three to four minutes following the intravenous injection of as little as 0.55 mg. of the homologous polysaccharide. The anaphylactic reactions are strictly type-specific. There is now ample evidence to support the view that protein-free, even nitrogen-free, carbohydrates may induce acute anaphylaxis in specifically sensitized animals.

Tillett and Francis have found that the injection of 0.01 mg. of specific polysaccharide into the skin of patients recovering from pneumococcus pneumonia may evoke an immediate local reaction in the form of a wheal surrounded by a zone of erythema. The cutaneous reactions develop rapidly within fifteen minutes and subside completely in from one to two hours; they are elicited only by the specific

polysaccharide derived from the same type of pneumococcus as that causing the infection in the patient. The capacity of the skin to react to the specific bacterial sugar is intimately associated with recovery and closely parallels the occurrence of type-specific antibodies in the patient's serum. The results indicate that this specific skin test has prognostic significance and may become of value in determining the therapeutic dosage of antipneumococcus serum.

Studies on "synthetic antigens" prepared by chemically combining derivatives of glucose and galactose with proteins have shown that even these simple sugars exert a determining influence on the immunological specificity of compounds of which they form a part. The newly acquired specificity of these artificially conjugated sugar-proteins is in each instance determined by the chemical structure of the carbohydrate irrespective of the protein to which it is attached. It is especially significant in the case of glucose and galactose that the two sugar derivatives differ from each other only in the spatial arrangement of the hydrogen and hydroxyl groups on a single carbon atom. It is a remarkable fact that the mere rotation of this carbon atom through an angle of 180° suffices to change completely the antigenic specificity of two substances otherwise chemically identical. In the case of these artificially prepared sugar-proteins, the two isomeric sugar derivatives can be selectively differentiated one from the other by serological methods. These observations on the immuno-chemistry of carbohydrates confirm the original studies of Land-

steiner on the specificity of azo-proteins and furnish additional evidence of the general dependence of immunological specificity upon the chemical constitution of the reactive substances. It is evident, therefore, that simple sugars, which by themselves are non-antigenic, may, when coupled to a protein, specifically determine the immune response of treated animals, and that the antibodies thus engendered reflect the orienting influence of the sugar radical on the specificity of the antigen as a whole.

From these results we were led to test the possibility of "synthesizing" an artificial bacterial antigen. For this purpose the capsular polysaccharide of type III pneumococcus was chosen, since it contains no nitrogen and in its present state of purity may be regarded as a definite chemical entity. Moreover, if results were obtained with this particular polysaccharide they would be the more significant, since the free substance by itself has never been found to elicit any immune response in rabbits and even the original bacterial cells from which it is derived fail in a majority of instances to incite specific antibodies in these animals. From a chemical point of view, the difficulty lay in synthesizing the appropriate derivative of this complex sugar. It must be one capable of being coupled to protein and one in which the chemo-specific groups of the polysaccharide are not masked by the chemical procedures. Dr. Goebel succeeded in synthesizing the amino-benzyl-ether of the type III polysaccharide and in coupling the diazonium derivative with a foreign protein namely, the globulin from horse serum.

This soluble antigen therefore has in common with type III pneumococcus only the specific capsular polysaccharide. Rabbits injected with this artificial antigen uniformly developed in their serum type-specific antibodies. The antiserum thus produced not only precipitates the original polysaccharide but agglutinates living cultures of type III pneumococcus and protects animals against infection with virulent organisms of the homologous type.

Knowledge of the chemical nature and significance of the capsular polysaccharides in pneumococcus infection and immunity led us to search for enzymes capable of decomposing these specific carbohydrates. A number of enzymes of animal and plant origin as well as cultures of various bacteria, yeasts, molds and soil actinomycetes, many of which were known to decompose cellulose and other complex carbohydrates, were tested without success. My associate, Dr Dubos, isolated from peat soil a bacillus which possesses an enzyme that acts specifically on the capsular polysaccharide of type III pneumococcus. From these bacilli the active enzyme has been extracted in soluble form. By technical procedures, active preparations of the enzyme have been purified and concentrated without appreciable loss in potency.

In view of the marked differences in the chemical composition of the various capsular polysaccharides, it is not surprising to find that the enzyme decomposes only the type III substance and has no effect upon any of the other bacterial sugars thus far tested. In this respect, the selective action of the enzyme is as specific as in the immune

reaction between the type III polysaccharide and its homologous antibody. The polysaccharide acted upon by the enzyme loses its serological specificity and is no longer precipitable by type III antipneumococcus serum. This enzyme not only acts on the chemically isolated sugar, but it specifically decomposes this substance in the native form in which it exists in the capsules of the living cells. When a sterile solution of active enzyme is added to a growing culture of type III pneumococci, the organisms lose their specific agglutinability and the soluble capsular polysaccharide is serologically no longer demonstrable in the culture fluid. Under these conditions, the enzyme decomposes the capsular substance as rapidly as it is formed without impairing the viability of the decapsulated organisms.

The action of the enzyme does not result in a loss of the function of elaborating the capsular substance, since pneumococci so treated promptly regain their capsules when transferred to an enzyme-free medium. The active enzyme, therefore, represents a specific agent which by itself is neither bactericidal nor bacteriolytic but which, by decomposing the capsular structure, completely alters the biological behavior of the bacterial cell.

In view of these findings, experiments were carried out to determine whether the enzyme would favorably influence the course of experimental infection in mice with type III pneumococcus. It was found that a single injection of an active preparation of enzyme protected mice against infection with a million times the number of virulent organisms invariably fatal

in the untreated animals. The protective action of the enzyme is type-specific, just as in the test tube it decomposes only the type III polysaccharide, so in the animal body it is effective only against infection with type III pneumococcus.

Experimental evidence indicates that in mice the enzyme also has a curative action when administered in the course of an infection already well established at the time of treatment. The administration of the specific agent as late as eighteen hours after the onset of infection has brought about the recovery of mice infected with multiple lethal amounts of a virulent culture of type III pneumococcus. Experiments carried out in collaboration with Dr Goodner and Dr Dubos have shown that the enzyme also has a marked curative action in the disease brought about by infecting rabbits intradermally with a highly virulent strain of type III pneumococcus. The experimental disease is characterized by the rapid development at the site of inoculation of an intense inflammatory lesion with spreading edema, marked cellular infiltration and hemorrhagic necrosis, accompanied by fever and the early invasion of the blood stream with increasing numbers of pneumococci. The infection ordinarily terminates fatally within three to four days in 95 per cent of untreated rabbits. Following the intravenous injection of an adequate amount of active enzyme the bacteremia promptly disappears, the

local lesion, freed of bacteria, undergoes the natural processes of healing, and recovery occurs in 95 per cent of the animals so treated.

The experimental results support the view that the primary action of the enzyme lies in its capacity to decompose the capsular polysaccharide of the invading pneumococci. The process of decapsulation brought about by the direct action of the enzyme strips the bacteria of their capsular defense and thereby exposes their naked and unprotected bodies to direct attack by the phagocytes of the host. Thus phagocytosis, ineffective against the encapsulated forms, now becomes the important mechanism in the final destruction of organisms from which the capsular substance has been removed by the action of the enzyme.

In this sense, the enzyme may be said to initiate a protective reaction, the successful issue of which depends upon the effective phagocytic response of the host. For these reasons, it at once becomes apparent that the curative action of the enzyme is subject to the limitations imposed by the variations that occur in the cellular defense of the infected animal.

These studies suggest that the capsule—long recognized as a defense mechanism on the part of virulent bacteria—is a decisive factor in determining the fate of pneumococci in the animal body and that this structure is vulnerable to attack by agents other than specific antibodies.

Presentation of the John Phillips Memorial Prize*

By S. MARK WHITE, M. D.
President of the American College of Physicians

DR. Avery, Fellows of the American College of Physicians, Associates and Guests

John Phillips was born in Welland, Ontario, February 18, 1879. With a personality marked by simplicity, directness, poise and a remarkable sense of relative values, he came in the fifty years of his life to a high place in medicine in this country. Work was his philosophy of life. He exemplified this, called by Osler the Master Word. His intimate friends tell us he appeared not to know how to play. His contributions to medicine and its literature were many, and were scholarly and sound. Elected to the Board of Regents of the American College of Physicians in 1923, he was active in its affairs in many and important ways. He arranged the programs for the Annual Sessions in Cleveland in 1927.

Valuable as we who knew him held his life to be, he held it as naught if it was needed in the succor of others. When disaster visited the Cleveland Clinic in 1929, he, Chief of Medicine, without thought of self, labored to save its victims. Giving his life on May 15, 1929, he left us a glorious example. The college has founded this annual prize to perpetuate his memory.

The purpose of this prize is to encourage work adding to our knowledge in Internal Medicine, this including not only clinical science but in addition all those subjects which have a direct bearing upon its advancement.

When in one of the Hippocratic writings, "The Law", we read, "There are in effect two things, to know and to believe one knows, to know is science; to believe one knows is ignorance", we are on the threshold of the conception of medicine as an art based on accurate observation, and as a part of the science of man. When many centuries later we follow William Harvey and René Descartes in "la nouvelle methode" of experimental science, we are preparing to wrest from nature some of her profoundest secrets. Induction, intuition, and deduction, served by the sometimes slow, painstaking methods of trial and error, lead us to an understanding of nature never suspected by the ancients. But here again we glimpse what they so plainly saw, "Life is short and the Art is long". Fifty years have passed since Robert Koch discovered the bacillus of tuberculosis. The conquest of the disease, though well under way, is not yet complete. In the meantime, yellow fever has been eliminated from the

*April 6, 1932

civilized world, through the efforts of a devoted band of scientists with its martyrs, even though the causative organism may be yet in doubt. Illustrations need not be multiplied.

Fifty years have passed since Friedlander found that capsulated cocci were present constantly in the exudate of pneumonia, and two years after that, Fraenkel demonstrated the causative relation of the pneumococcus to the disease. Our conquest of pneumonia has scarcely begun. We are beginning to see it as through a glass, darkly, however. All honor then to the men, who step by step, are treading the paths that will eventually lead to the hiding place of the pneumococcus, and who by the processes of science, though they be slow and painstaking, are discovering how to strip it of its protective covering.

The committee having in charge the award, in seeking a candidate, selected an advisory group of sixteen members of the College, each prominent in some certain aspect or field of medicine. The suggestions made by each of these, and by the members of the committee, were

listed and then sent out to the two groups, with the request that each man would indicate his first, second and third choice from amongst that list. Twenty-five of the votes went to Dr Avery.

The committee, therefore, through its chairman, Dr James H. Means, recommends the award, "To Dr O. T. Avery for the series of studies upon the pneumococcus in which he has played a leading rôle, beginning with the discovery of the type specific soluble capsular polysaccharides and culminating in the discovery of a bacterium producing an enzyme which splits the polysaccharides of type III pneumococcus in vitro, thus rendering it susceptible to phagocytosis and thereby protecting the animals which are infected with it." Dr Avery, you are the first recipient of this annual award. As evidence of appreciation of your industry, your devotion to Science and your scholarly attainments we present you, in the sum of \$1500.00, with this, the John Phillips Memorial Prize of the American College of Physicians.

Physical and Physiological Aspects of Arteriosclerosis and Hypertension*

By CARL J. WIGGERS, M.D., F.A.C.P.,
Cleveland, Ohio

INTRODUCTION

THE subjects of arteriosclerosis and hypertension have been extensively studied and even more extensively discussed by the clinician, pathologist, therapist and experimentalist, each naturally, according to his own point of view. But results of physical and physiological investigations have been more or less entombed in library stack-rooms, at least to my knowledge they have not been reviewed in such a form as to make the facts easily available.

My own venture in attempting to review a topic in which so many gaps still exist is actuated by our need for survey of the known physical and physiological consequences of arterial disease. Such an adventure is of triple value: it places the essential known facts in orderly array, it reveals the gaps and questionable evidence and supplies a working basis from which new physiological investigations may proceed. Indeed, such a systematic

survey and critical evaluation of existing theory and fact forms a natural prelude to an interpretation of those experiments which Nature chooses to make on animals and man, and which are designated by the term, Disease.

PHYSIOLOGICAL FACTORS IN HYPERTENSION

Two primary vascular changes may be concerned in hypertension, viz., (a) alterations in the elastic properties of the large arteries which serve as physical buffers to the capillary flow and (b) changes in the lumen and resistance of the smaller arterioles which act in the capacity of stopcocks regulating the outflow from the arterial tree. In addition, secondary changes in the action of the heart supervene and complicate the dynamic picture. When, as in this instance, the heart and circulation are affected by a number of different factors it becomes confusing, if not quite hopeless, to evaluate the share that each element contributes. In such instances, physiologists frequently adopt the expedient of studying the changes in the heart and circulation when only a single factor alters at a time. We shall utilize this method in analyzing the hypertension problem.

*From the Department of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio. Read before the American College of Physicians, San Francisco, April 6, 1932.

THE EVALUATION OF ARTERIAL ELASTICITY

Studies on Excised Vessels The elasticity of tubular structures such as arteries is usually determined by measuring the increase in cubic contents when the internal pressure is raised a definite amount. The ratio, pressure increase to volume increase ($\frac{dp}{dV} V$), is designated the *volume elasticity coefficient* (E_v). Obviously, such a coefficient increases inversely as elasticity and directly as rigidity.

Physical tests have demonstrated that arteries are not equally distensible at all internal pressures, on the contrary, their distensibility decreases progressively as internal pressure is raised. A curve in which pressures as abscissae are plotted against volumes as ordinates therefore assumes a hyperbolic form, convex to the abscissae (figure 1, A). When medium sized arteries, such as the carotid, brachial or radial are studied, it is often found that the reactions differ both quantitatively and

qualitatively in repeated tests. Two other forms of curves, illustrated by B and C in figure 1, are often obtained. Each of these has, indeed, been advocated as representing the true volume-elasticity curve of arteries. MacWilliam (1902) concluded that these variations are due, in large part at least, to variable degrees of muscular contraction. According to his studies, moderate muscular contraction hinders stretching at lower internal pressures only, hence the elasticity coefficient follows an S-shaped curve (B). If, however, the vessels are firmly contracted, the muscular force opposes distention at all ranges of internal pressures, hence a straight line or concave elasticity curve (C) is the result. It is obvious that the excursion of peripheral arteries such as the radial and perhaps the brachial may not be governed solely by internal pulse pressure variations but by the degree of muscular contraction as well.

When an artery becomes less elastic through sclerotic processes or chemical

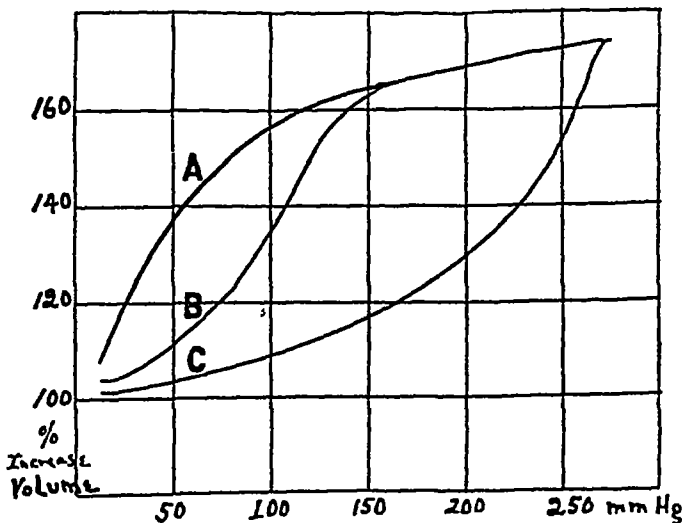


FIG 1 Volume elasticity curves of medium sized arteries. A, relaxed vessels, B, moderately contracted vessels, C, strongly contracted vessels

treatment, its distensibility under equivalent pressures is not merely decreased but the form of the extensibility curve also changes. Obviously some other factor, that may be spoken of as the elastic "personality" of the vessel, is altered.

Frank (1927) designated this by q in the equation $E = E_0 + q\sigma^2$, in which E_0 denotes the residual elastic resistance of unstretched vessels and σ the specific tension per unit cross-section area

After mathematical treatment of the problem (1920, 1928) Frank (1927), in association with Mays and Hochrein, reported experiments on rings of aortas obtained post-mortem from individuals of different ages. Such central vessels have the advantage of giving constant responses because the experiments are not complicated by the effects of muscular contraction. These data have been plotted, using E values as ordi-

nates and σ values as abscissae (figure 2). A glance shows that in young persons arterial rigidity (E) increases very little at lower tensions but trends rapidly upward at higher tensions (σ). In case of aortas from older subjects, on the contrary, the lines begin to curve upward at progressively lower tensions and, moreover, rise with a steeper gradient until in very old age they become almost straight lines from the start. Such curves indicate that while the residual elasticity of arteries (E_0) does not alter with age, their extensibility decreases rapidly with increasing tensions and more especially at lower tensions. Graphs such as these give a qualitative and objective picture of the changes concerned in ageing of the arteries. Since the coordinates of each curve can be expressed mathematically as a rational function of their parameter—i.e., q in Frank's formula—it is possible to cal-

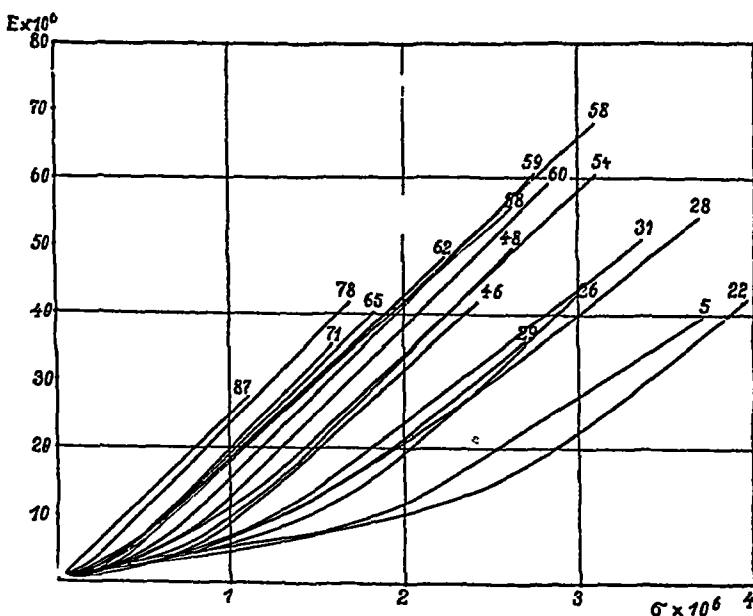


FIG 2 Curves showing the elastic coefficients (E) of aortas at different specific tensions, (σ) at ages directly indicated on the chart. E and σ , expressed in 10^6 dynes, a unit which corresponds approximately to pressure exerted by an atmosphere per cm^2 (after Frank)

culate values for q^* and to express the age characteristics in a quantitative fashion, as in figure 3. A consideration of such graphs led Frank to the conclusion that while the residual elasticity (E_0) scarcely alters with age extremes (5-87 years) the parameter q increases more than sixfold

ing to the classical formula of Moens ($V = K\sqrt{g \frac{Ea}{sd}}$) the pulse wave velocity (V) varies directly as the square root of gravity (g), the elasticity coefficient (E), and the arterial wall thickness (a), and inversely as the square root of the specific gravity of

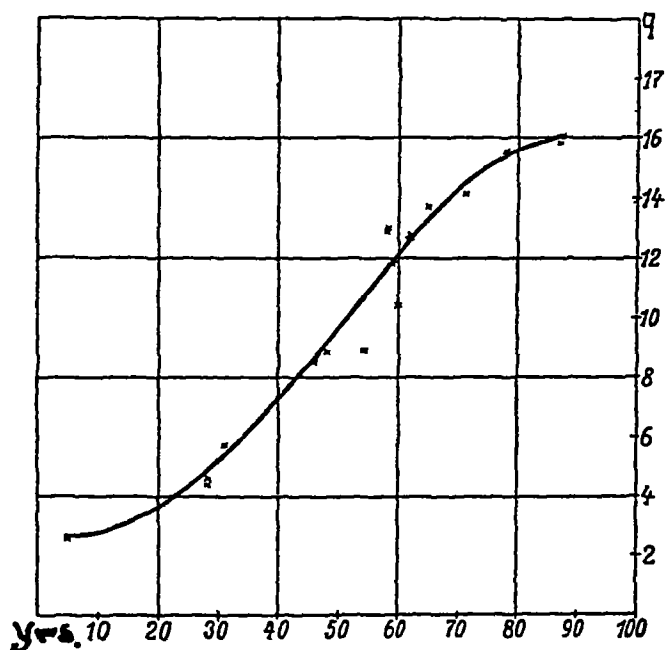


FIG 3 Curve expressing mathematically the elastic characteristics (q) of the aorta at different ages (abscissae) (after Frank)

It can safely be predicted that systematic use of this method in post-mortem studies of large arteries from subjects who had arteriosclerosis and hypertension would yield part of the information still needed to explain both the cause and the dynamic effects of hypertension

Studies on Vessels in Situ Accord-

*Since the parameter q has no absolute value it has been given the arbitrary value 15 when specific tension equals 1.5×10^6 dynes. The formula expressing the elasticity coefficient at this pressure then becomes $E_{1.5} = E_0 \times \sigma_{1.5}^2$

blood (s) and the diameter of the vessel (d). Assuming all factors except E to remain constant or to be inconsequential, an inverse relation obviously exists between pulse velocity and arterial elasticity

It is therefore not surprising that many investigators have attempted to study the elastic condition of arteries *in situ* by measuring pulse velocities. While there appears to be general agreement in the conclusion that the pulse velocity progressively increases with age, an examination of the many

data upon which such statements are based reveals many discrepancies both as to what constitutes a normal velocity and as to the magnitude of the increase with age. Figure 4 shows velocities reported by three groups of workers in comparison with values calculated by Frank on the basis of elasticity studies of human aortas. The great differences shown require no further comment. Likewise, while the majority of observers claim that the pulse is propagated faster in cases of demonstrated arteriosclerosis, nephritic hypertension, etc. (Friberger, 1912, Munzei, 1912), Sands (1925) was unable to corroborate these results. My own observations confirm the conclusion that the pulse velocities encountered in patients with hypertension certainly fall within the ranges found yearly in young, healthy medical students.

The variable results arrived at by different investigators are partly due to the methods and procedures employed

in estimating pulse velocities; partly also to the fact that pulse velocity is affected by the size of vessels (Bazett and Dyer, 1922; Sands, 1925) and by the height of diastolic pressure (Frank, 1927, Bramwell, Hill, McSwiney et al., 1922-1923). Improvements in technical methods for pulse registration have reduced to a minimum the errors incident to accurate calculations of pulse delay between two points. Unfortunately, it remains just as difficult to measure with exactness the arterial distance traversed by the pulse wave. The possibility of error thus introduced becomes even greater when vessels are tortuous. The variations in size of vessels resulting from muscular contractions or pathological processes are also beyond our present means of study and evaluation (cf Lyon and Sands, 1924).

Bramwell, Hill and McSwiney (1922, 1923, 1924) have made earnest attempts to take variable diastolic pressures into account and to this end have

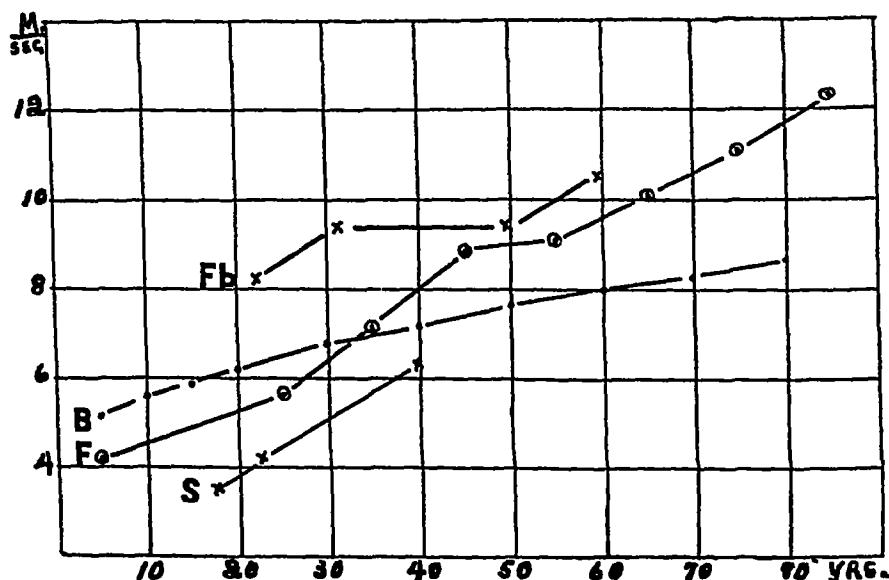


FIG. 4 Chart giving pulse velocity data at different ages according to Friberger (Fb), Bramwell and Hill (B), Sands (S), compared to calculated velocities of Frank (F) for internal pressures of 100 mm Hg

introduced an ingenious yet simple method by which the *effective* diastolic pressure in a short length of artery can be altered at will. This was accomplished by applying a positive or negative counter pressure over a brachial or radial artery through an elastic cuff or chamber and calculating the velocity of the pulse wave in the short length of vessel submitted to such positive or negative pressures. In this way, the pulse velocities at pressures above and below existing diastolic pressures could be calculated according to the formula

$$V = \frac{d}{y-x} \left(\frac{1-d}{1} \right)$$

where x equals transmission time between two points distant 1 from one another and y the time between same points when a bandage of length d is applied. By applying a simplified formula,

$$\frac{\text{percentage increase in volume per mm rise of pressure}}{127} = \frac{127}{\text{Velocity in meters/sec}},$$

the extensibility at different diastolic pressures could be determined and plotted in the form of curves. Finding good agreement between average velocities in vessels *in vivo* and others on isolated arteries, Bramwell, Hill and associates concluded that it is possible to evaluate changes in elasticity of vessels *in situ* by such means.

The method, however, appears to have several shortcomings. (1) The actual length of artery compressed and hence the pulse velocity in it cannot be determined with great exactness, (2) the extensibility curve derived applies only to the vessel examined and not to the aorta or arterial system as a

whole, and (3) the extensibility curves of similar arteries are apparently not the same in normal individuals. Thus, Hemmingway, McSwiney and Allison (1928) recently found great differences, both in pulse velocities and extensibilities of normal brachial arteries. A series of these curves, reproduced in figure 5, indicates that the arteries of normal individuals fall into three groups, viz, super-extensible (S), normal (N) and hypo-extensible (H) and furthermore that the mean pulse velocity at corresponding effective pressures (lower set) varies a great deal.

I have set forth briefly the difficulties that discourage the use of pulse velocity determinations in evaluating the elastic state of vessels *in situ* not with the purpose of detracting from the sincere attempts made to overcome great physical difficulties, but rather to

give you an idea of the obstacles that still remain to be surmounted.

THE FUNCTIONAL NATURE OF INCREASED PERIPHERAL RESISTANCE

Morphological changes in the peripheral arterioles with reduction or obliteration of their lumen rarely if ever account entirely for the increased peripheral resistance encountered during hypertension. Endarteritis is rarely universal; not infrequently it is limited to individual organs such as the kidneys, pancreas, spleen, etc. Moreover, even after mechanical deletion of large portions of the natural circu-

lation, physiological compensatory mechanisms, both nervous and mechanical, are able to reestablish arterial pressures at approximately normal levels. For example, it is possible in dogs to ligate one common carotid, both subclavian and internal mammary arteries and, in addition, the aorta above the renal arteries without causing a rise of blood pressure that lasts more than ten or fifteen minutes.

Consequently, the conclusion appears justified that increased peripheral resistance sufficient to bring about prolonged or permanent elevation of pressures must be due either (a) to excessive generalized functional contraction of arterioles or (b) to failure of

the reflex mechanisms which normally moderate blood pressures. The agents which cause such vascular constriction and the mechanisms involved remain shrouded in mystery; indeed, it is not improbable that they are many and varied. Time is lacking to review the many chemical, hormonal and nervous theories that have been advanced to account for the generally contracted state of peripheral arterioles. Fortunately, this is not vital, however, as the reader may refer to the excellent monograph of Gager (1931) for a discussion of this aspect of the subject. The possibility that unbalanced reflexes rather than specific chemical stimulations of arterioles or their controlling nerve

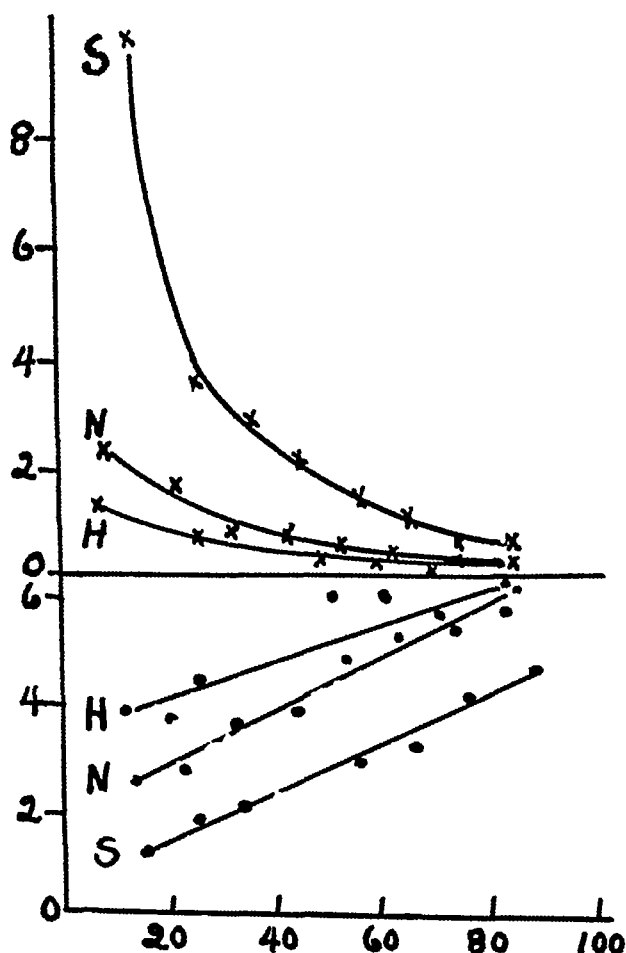


FIG 5 Graphs showing arterial extensibility (upper curves) and pulse velocities (lower curves) in normal individuals at effective diastolic pressures indicated on abscissae S, super-extensible type, N, normal type, H, hypo-extensible type—(after plots from McSwiney et al)

centers may play a rôle in some forms of human hypertension is suggested by recent experimental work. Denervation of the sinus caroticus and section of aortic nerves can provoke a state of hypertension accompanied by notable increase in cardiac size (Koch, Mies and Nordman, 1927, Regniers, 1930). Mechanical obstruction to flow in abdominal viscera and perhaps in the heart may likewise set vasomotor reflexes in operation which if uncompensated may result in persistent hypertension (cf Hering, 1930).

HEMODYNAMIC AND CARDIODYNAMIC EFFECTS OF INCREASED ARTERIAL RIGIDITY

Arterial Pressures and Flow

Mathematical calculations and physical experiments lead to the conclusion that increased rigidity of large blood vessels causes an elevation of systolic and a decline of diastolic pressures at a constant cardiac rate and output. The arithmetical mean pressure is reduced somewhat. Fahr, Davis, and Spittler (1931) have demonstrated that similar changes occur in a heart-lung preparation so arranged that the volume-elasticity coefficient of the arterial system could be increased or decreased at will. However, the pressure changes reported were doubtless exaggerated a great deal through the maximum and minimum valved mercury manometers employed.

I have recently reinvestigated the circulatory effects produced when the elasticity of the aorta was decreased by treatment with formalin. The aorta from a large dog, after removal from the body and ligation of all branches, was inserted into an artificial circuit

in which pressure variations resembling those found in normal animals were reproduced artificially. In such a system the pressure head, heart rate, periods of ejection and peripheral resistance could be kept constant while the elasticity of the aorta was changed by perfusion with formalin solution. Optically recorded pressure curves before and after formalinizing the aorta are shown in segments D, E and F of figure 6. They demonstrate that the more rapid decline of pressure during diastole and the consequent lowering of diastolic pressure are the only changes as long as the pressure head remains constant. The explanation is simple. Through a reduced expansion of the aorta by an equal pressure head, less blood is accommodated during mechanical systole and a larger volume moved forward. Consequently the tubes contain less fluid at the beginning of mechanical diastole and reach their normal state more rapidly, with the result that arterial pressure falls quickly and to a lower level. The stream distal to a peripheral constriction, i.e., in the capillaries, becomes less and less constant as elasticity diminishes and with very rigid vessels acquires a pulsating character. The minute flow also decreases. Such physical experiments demonstrate how a capillary pulse and collapsing arterial pulse can be dynamically produced without change in peripheral resistance or without occurrence of valvular insufficiency. The practical conclusion is derived that the collapsing character of clinical pulses during aortic insufficiency becomes greatly intensified when sclerosis of the aorta coexists.

Dynamic Effects on Left Ventricle

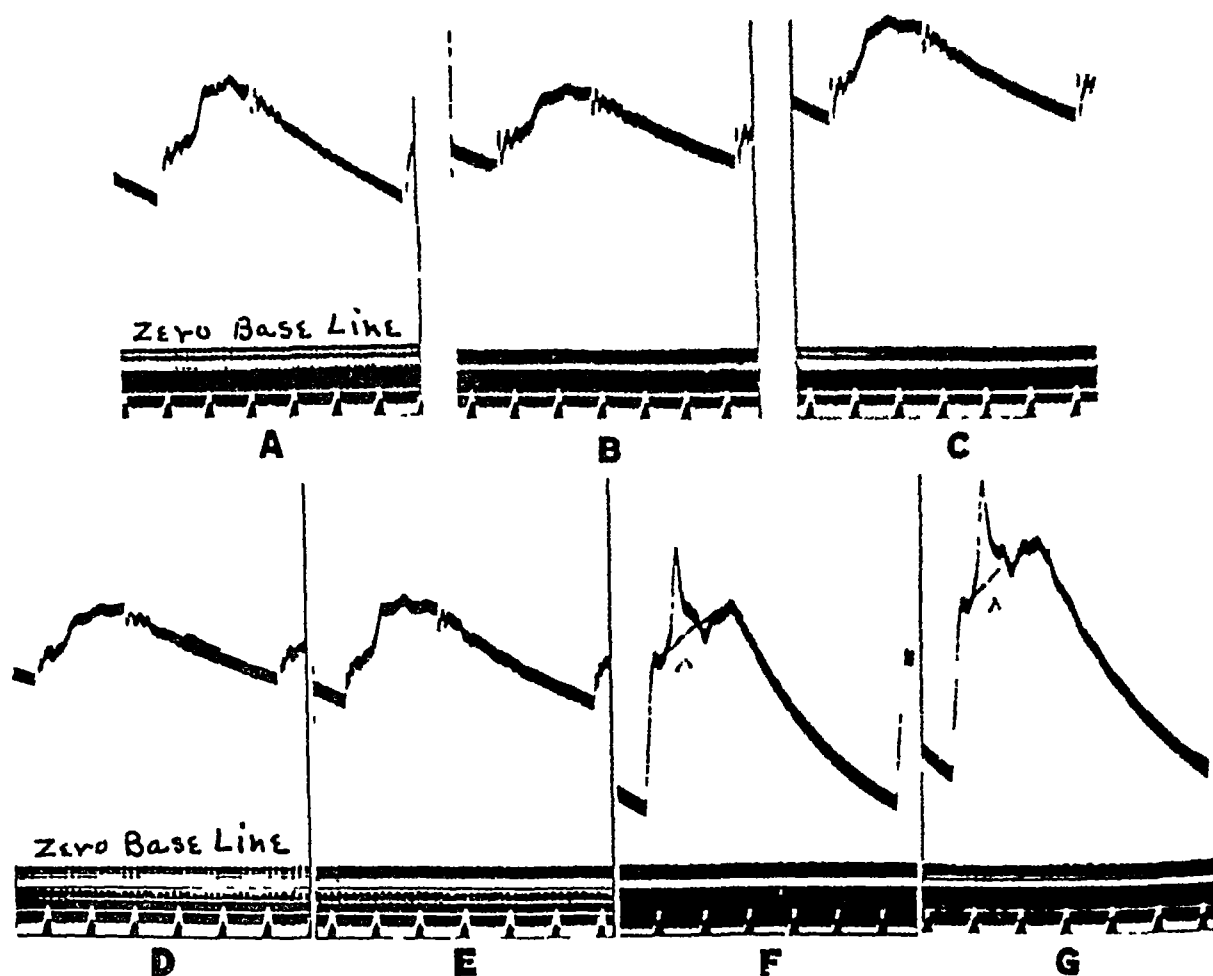


FIG 6 Aortic pressure curves from a dog's aorta in an artificial circulation machine A, control conditions, minute volume, 630 cc, B, after increased peripheral constriction, minute volume, 350 cc, C, after raising pressure head, minute volume, 420 cc D, same conditions as B, E, 10 minutes after applying formalin to aorta, minute outflow 290 cc, F, 3 hrs after formalin treatment, minute outflow 240 cc, G same conditions as F but with increased systolic pressure head, minute outflow 310 cc Peaks x are accentuated waves (possibly reflected waves) superimposed on fundamental forms Time 1/5 sec

The total internal energy transformation during each heart beat is largely degraded into heat, less than 20 per cent manifesting itself as useful external work

The work of the left ventricle is conveniently, though somewhat roughly, calculated as the product of mean pressure and quantity of blood ejected Using such a formula, Fahr, Davis and Spittler (1930-31) concluded from experiments on heart-lung preparations that since neither factor changed significantly, the external work of the heart is practically unaffected through

an increased elasticity coefficient of the arterial system

The total energy utilization can be found directly only from studies of oxygen consumption by the heart Such determinations still need to be made Starling and Visscher (1927), however, observed quantitative relations between changes in oxygen consumption and diastolic size and Fahr et al (1931) noted that the diastolic size remained unaltered when the volume elasticity coefficient of the arterial system was increased Therefore they tentatively concluded that the total en-

ergy consumption of the heart is little, if at all, affected

These deductions, however, square neither with *a priori* considerations nor with physical experiments. Any augmentation of arterial systolic pressure obviously presupposes a corresponding elevation of left ventricular pressure. It is difficult to visualize how this can come about without additional expenditure of energy if, as experiments indicate, systolic discharge remains the same. Physical tests show definitely that the minute volume flowing through less elastic tubes can be restored to normal only by increasing the pressure head. Thus in the experiment illustrated by segments D, E and F, figure 6, the minute outflow decreased progressively from 340 to 240 c c, but by elevating the pressure head and thereby both systolic and diastolic pressures as shown in segment G the outflow was increased again to 310 c c. The faultiness of Fahr, Davis and Spittler's recent conclusions appears to arise from use of an arithmetic mean pressure in calculating the work of the left ventricle and in ignoring entirely the velocity factor. Katz (1932) has recently again pointed out how great and variable the error may be, even when mean pressure and mean velocity are both used in work calculations. The tendency is to under-estimate both the pressure and velocity energy and to alter their distribution so that the per cent calculated as kinetic energy seems less than it really is. On a previous occasion Fahr (1927) himself recognized that such calculations are only approximations and suggested the integral

$$\int_{P_1}^{P_2} p \, v \, d + \frac{sv^2}{2g}$$

Using this integral, Fahr (1927) also arrived at the conclusion on theoretical grounds that arteriosclerosis increases the work of the left ventricle but only insofar as it necessitates increased systolic pressures.

A critical evaluation of existing theory and fact therefore makes it improbable that an increased elasticity coefficient of the aorta is without effect on the total energy expenditure or external work of the left ventricle, though it is probable that the magnitude of the increase need not be very great with the degree of rigidity ordinarily attained.

Hemodynamic and Cardiac Effects of Increased Peripheral Resistance
Increased arteriolar resistance affects hemodynamics primarily by reducing the minute efflux from the arterial system. As a result, systolic and diastolic pressure are both elevated and the amplitude of the pressure variations is reduced. In other words, the effects on pulse pressure are just the reverse of those produced by decreased elasticity of large vessels. The significance of the physical changes in systolic and diastolic pressures are demonstrated by experiments on a dog's aorta. As shown in figure 6, A and B, augmented peripheral resistance decreases the rate at which pressure declines during diastole and elevates the diastolic pressure when the pressure head (i.e., systolic pressure) is kept constant. Coincident with these changes in pressure the peripheral outflow decreased from 630 to 350 c c per minute. When the pressure head is elevated, both systolic and diastolic pressures rise together but the pulse pressure still remains less than normal. As illustrated in figure 6, C, even this elevation of

pressure head was unable to restore the minute outflow to normal, for it was only 420 c c per mm. at the time this tracing was recorded. Such physical experiments demonstrate clearly that the rise in diastolic pressure reflects primarily the magnitude of the peripheral resistance change and that a considerable elevation of systolic pressure is needed in order to restore the capillary bloodflow to normal

The manner in which the heart accomplishes this can fortunately be studied in animals whose peripheral resistance is acutely increased either mechanically by compression of the abdominal aorta or more physiologically by generalized vasoconstriction. The latter is easily accomplished reflexly by stimulating the central end of a vagus nerve. The changes in central pressure pulses produced by such stimula-

tion are illustrated by segments A, B and C in figure 7. We note that contrary to physical experiments, the pulse pressure increases and that systolic pressure rises more than diastolic. The preliminary vibration (a) occurring during the isometric periods becomes more intense and the height of the primary upstroke (b) increases. All of these characteristics clearly indicate that the ventricular contractions were more vigorous.

The mechanisms by which this is accomplished were studied by Katz and myself.* These investigations demonstrated that increased peripheral resistance causes an immediate but transient decrease in systolic discharge

*For details cf Wiggers, *Circulation in Health and Disease*, 1923, p 113, *Pressure Pulses in the Cardiovascular System*, 1928, p 132

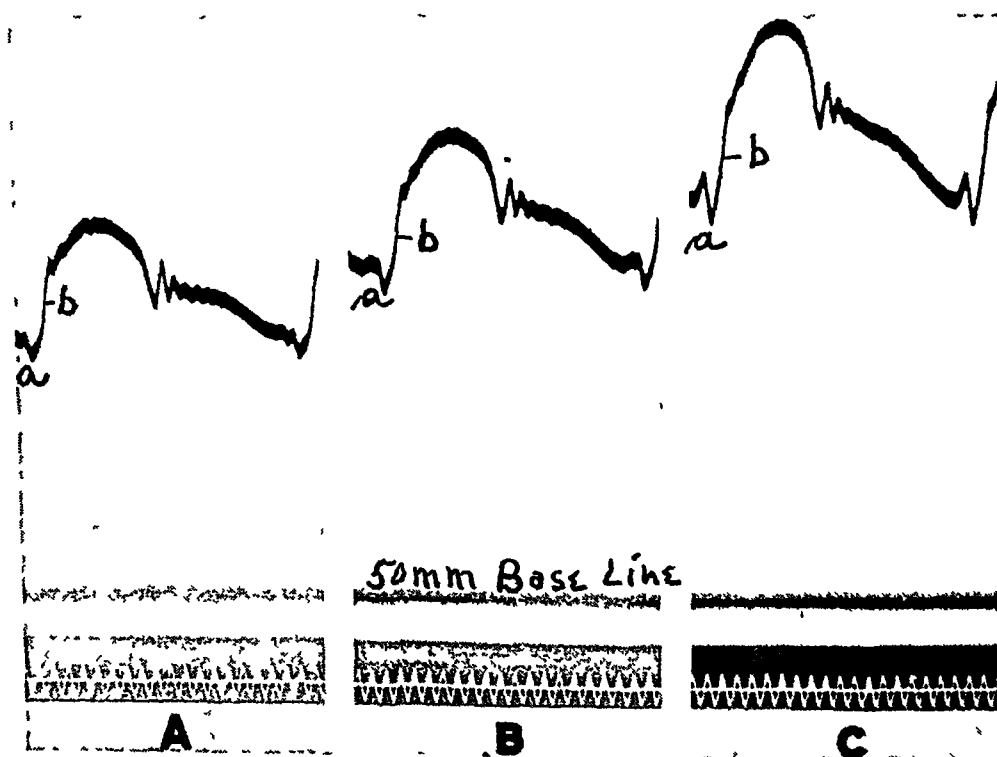


FIG 7 Subclavian pressure curves recorded by optical manometer from a dog. A normal pressure pulse, B and C at various stages during increased peripheral resistance produced by central vagus stimulation. Time 02 sec

with the conversion of more kinetic energy into pressure energy. The residual blood which thus accumulates from beat to beat, added to normal inflow from the left auricle, quickly increases diastolic ventricular size and elevates the initial tension. This acts as a stimulus to cardiac muscle, in consequence of which systolic volumes again equal or even exceed the normal, depending on the intensity of the peripheral change.

Wiggers and Katz (1928) have further studied how the economy of ventricular effort is affected under such conditions. This was done by determining the ratio between the static effort and dynamic effort of the left ventricle during the period of ejection. To do this, we calculated by analysis of optical pressure curves how much of the total pressure energy during the ejection period is required to support the arterial pressure in the aorta statically and how much is stored during systole for conversion into energy of flow during subsequent diastole. Our results show that increased arterial resistance not only augments the external work of the heart but also decreases the economy of effort. We also found, however, that the increased diastolic size and initial tension supplies a mechanism whereby the economy of effort is approximately restored to normal.

Summarizing, the accumulation of residual blood which temporarily follows increased peripheral resistance acts successively to increase the diastolic size and initial tension and to restore both the systolic output and the economy of effort to normal. Through these physiological compensatory

mechanisms systolic arterial pressure is elevated until the capillary volume flow is again normal.

PHYSIOLOGICAL FACTORS IN CARDIAC HYPERTROPHY

Growth implies increased metabolism. Increase in bulk of muscular elements, i.e., hypertrophy, must therefore be preceded by increased metabolic rate. The experimental results of Starling and Evans and Starling and Visscher make it extremely probable that, as far as the heart is concerned, oxygen consumption is related solely to changes in diastolic volume. Hence, of the many theories proposed to explain cardiac hypertrophy, the conception that it is caused by a previous increase in initial tension and diastolic stretch appeals most to a physiologist. Since only a moderate increase in peripheral resistance is required to produce such changes in diastolic size and since the elasticity coefficient of the larger vessels must be considerably augmented to effect a much smaller ventricular distention, the conclusion follows that alteration in caliber of peripheral vessels is ultimately the predominant factor responsible for the left ventricular hypertrophy so common in patients with persistent hypertension.

This is not the occasion to discuss the many theories proposed to explain ventricular hypertrophy. It may be stated in passing, however, that the view of Holman (1925) which associates hypertrophy with movement of increased minute volumes by the ventricle, certainly cannot account for hypertrophy secondary to hypertension. Neither animal experiments nor

observations on patients with hypertension give any evidence that the minute volume is significantly increased (see below)

Hypertrophy is so commonly regarded as a pathological and harmful process that its beneficial character is generally forgotten. The physiologist looks upon hypertrophy as a normal functional response to increased stretch, regardless of whether this is secondary to physiological or pathological changes in the circulation. In a sense, the normal left ventricle is physiologically hypertrophic. At birth the weights of the two ventricles are very nearly equal but, owing to a progressively greater peripheral resistance and diastolic stretch, the left ventricle slowly increases in bulk. The question may therefore be raised whether an additional increase in left ventricular bulk during hypertension cannot also be considered a physiological rather than a pathological reaction. It is true that deleterious influences primarily responsible for changes in diastolic size and hypertrophy may also effect the myocardium, producing structural differences in heart muscle cells which are superadded to, but not fundamentally a part of, the hypertrophic process *per se*.

THE PHYSIOLOGY OF CLINICAL HYPERTENSION

By far the majority of clinical investigators are rapidly arriving at the conclusion that changes in arteriolar resistance are mainly, if not solely, responsible for the hemodynamic alterations in clinical hypertension. This view is summarized with great positive-

ness, for example, by Weiss and Ellis (1930).

"A satisfactory explanation of the dynamics of the circulation in patients with hypertension is that due to the abnormally accentuated arteriolar resistance, a high arterial and arteriolar pressure is essential to establish the normal capillary bloodflow pressure in the vital organs. The measurements and observations do not bear out the observations that loss of elasticity of the great arteries, or increased cardiac output or increased circulatory volume - - - is responsible for the pressure of hypertension."

We have substantial experimental evidence for the conclusion that sclerosis of large central arteries, on one hand, and increased peripheral resistance on the other hand not only affect the left ventricle to different degrees but that they produce directly opposite effects on arterial pulse pressures and diastolic pressures as well. With this as a criterion we may properly inquire whether clinical forms of hypertension fall naturally into two such physiological groups or whether a combination of peripheral and central effects generally obtains. In scanning the records of patients with hypertension in the wards of Lakeside Hospital with the view of selecting certain types for more detailed physiological study I am continually impressed with the fact that the majority of subjects have large pulse pressures and high diastolic pressures. Except when complicated by aortic leaks, the patient with low or even normal diastolic pressure readings is rare indeed. These personal impressions are confirmed by a review of cases of hypertension reported in the literature. Let us take several examples. Hochrein (1928) tabulated 66 cases, exclusive of those with auricular

fibrillation In 58 of these, pulse pressure exceeded 58 mm , in 21 cases it ranged between 58 and 80 mm , in 22 cases, between 80 and 100 mm , and in 12 cases, between 100 and 135 mm In none of the 66 instances reported was diastolic pressure below 80 mm

tology and pathology can easily be duplicated from many other sources

The following simple tabular summary comparing clinical blood pressure observations with experimental reactions in which one factor is varied at a time is interesting

BLOOD PRESSURE CHANGES IN HYPERTENSION

	EXPERIMENTAL INCREASE IN RIGIDITY OF LARGE ARTERIES	EXPERIMENTAL INCREASE IN PERIPHERAL RESISTANCE	CLINICAL HYPERTENSION
SYSTOLIC PRESSURE	High	High	High
DIASTOLIC PRESSURE	Low	High	High
PULSE PRESSURE	Large	Small	Large

Hg In 34 cases it was between 99 and 109 mm , in 21 cases, between 110 and 134 mm , and in 6, above 135 mm Similar data from 27 patients reported by S Weiss and Ellis (1930) reveal pulse pressure ranges from 58 to 80 mm in 9 cases, from 80 to 100 mm in 7 cases, from 100 to 145 mm in 10 cases, and a value of 205 mm in 1 case Of these, one had a diastolic pressure of 68 mm , 8 had diastolic pressures between 90 and 109 mm , 16 between 110 and 135 mm , and 2 were 139 and 160 mm , respectively Twenty-four cases of hypertension tabulated by Feil and Katz (1924) show similar though less pronounced increases Diastolic pressures were 85 mm in one case, between 90 and 109 mm in 4 cases, between 110 and 135 mm in 10 cases, and between 136 and 175 mm in 9 cases However, pulse pressures ranging between 35 and 50 were reported in 7 cases, between 60 and 80 mm in 9 cases, between 80 and 89 mm in 5 cases, and between 90 and 110 mm in 3 cases

Such uniform and consistent pressure data from patients representing great variety as to etiology, symptoma-

It suggests forcibly that the experiments which Nature is accustomed to perform on patients generally combine alterations in elasticity of central vessels with increased resistance in peripheral arterioles, the large pulse pressure being a reflection of the greater rigidity of vessels and the high diastolic pressure, of the peripheral resistance change

If this is true, subclavian pulse tracings from patients with hypertension should display deviations from normal which resemble those of segments E, F and G of figure 6, rather than those of segments B and C of the same illustration This accords with my findings in a limited number of patients studied in Lakeside Hospital Figure 8 shows two sets of such tracings, B and C from patients with hypertension, and A from a normal medical student

The tracings of curves B were obtained from an individual without palpably thickened arteries and in whom all clinical signs pointed to increased arteriolar resistance as a cause of the high blood pressure While central and peripheral pulse curves re-

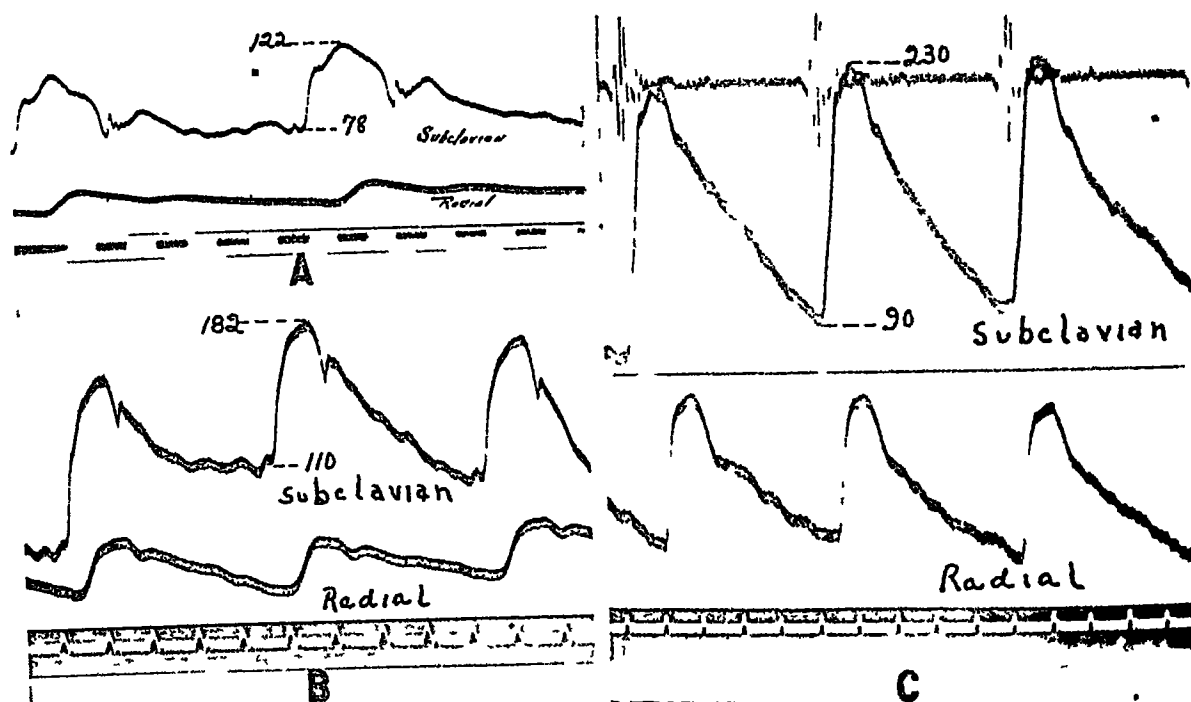


FIG 8 Three sets of human subclavian pulses (S) and radial pulses (R), A, normal subject, B, hypertension, essentially peripheral origin, C, hypertension, from patient with palpably sclerotic arteries Systolic and diastolic pressures marked directly on curves in each case Time in 1/5 sec

tain many characteristic features of normal curves, the rapid decline of the subclavian pulse curve after the incisura resembles the curve of segment E, figure 6, rather than that of segment B or C. The radial pulse also shows a sharper incisura than it is customary to find in normal pulses. Reflected waves such as are commonly superimposed on normal central pulses (A) are conspicuously absent. Consequently, despite contrary clinical evidence, anyone accustomed to curve analysis cannot conclude otherwise than that some decrease in arterial elasticity must have contributed to the changes in pulse form.

In the great majority of cases examined, however, the evidence is still more conclusive. The records reproduced as figure 8, C, were taken from a man 72 years of age. The subclavian and radial arteries were hard and

thickened and the former definitely enlarged. The central subclavian pulse is characterized by the steep ascent, by the short period of systolic ejection, by the altered contour of the systolic summit, but chiefly by the great decline of pressure following the incisura. The curves clearly resemble those of G in figure 6, not those of C in the same illustration.

The radial pulse curves fail to show the customary transformation of the pulse in its transmission to the periphery, on the contrary, its contour resembles remarkably that of the subclavian. The incisura is marked and no dicrotic wave is apparent. Such a propagation of pulse waves to the periphery could be possible only through very rigid vessels.

Summarizing, the large pulse pressures, high diastolic pressures and characteristic pulse curves exhibited by

the majority of patients hospitalized as a result of hypertension definitely favor the view that alteration in elasticity of large vessels modifies and often dominates the hemodynamics of the circulation. This in no wise precludes the coexistence of increased arteriolar resistance, nor does it invalidate the generally accepted belief that the latter is the primary disturbance and chiefly responsible for the cardiac hypertrophy.

Before our conclusion can be finally accepted, however, it is necessary to exclude the possibility that the large pulse pressure and excessively high systolic pressure are not due to an increased systolic output, a possibility that is given extra weight by the facts that a hypertrophied left ventricle exists clinically and that an increased systolic discharge consistently occurs in acute experiments on animals (cf figure 7). The evidence against such a possibility can be stated briefly.

1 The majority of investigators (Lauter and Baumann, 1928, Burwell and Smith, 1929, S. Weiss and Ellis, 1930, Ernst and R. Weiss, 1929, Hochrein, 1928) have been unable to demonstrate increased minute volumes in patients with hypertension, by means of gasometric methods.

2 The venous pressures do not appear to be elevated (Hochrein, S. Weiss and Ellis) and the blood volumes are apparently not increased (S. Weiss and Ellis).

3 The duration of systole in relation to cycle length is also not increased (Feil and Katz) as might be expected to be the case were the systolic discharge greater.

4 The changes in contour of the

central pulse are not those that would be expected were increased systolic discharge the chief factor concerned. It is necessary only to contrast curves of figure 8, B and C, with those of figure 7, B and C, in which changes in systolic output were alone superadded, in order to become convinced on this point.

Careful evaluation of the experimental and clinical evidence therefore leads to the conclusion that the circulatory changes in clinical hypertension are usually produced by the combined effects of increased peripheral resistance and decreased elasticity of the aorta.

Physiological Principles in Treatment Physiologically, hypertension must be looked upon as a compensatory reaction designed to restore a normal blood supply to the tissues. As already explained, the elevation of systolic pressure is the effective force, while increase of diastolic pressure is largely a resultant of the peripheral and central vascular changes. If the physiological conception that hypertension is Nature's method of assuring an adequate blood supply to the tissues, could gain firmer root in the doctor's mind and through him be relayed to his patient, it would do much to dispel that feeling of despair and impending doom so common in the layman who learns that his blood pressure is "high." Judiciously used, the physiological conception can do much to supplant pessimism by optimism, both in patient and doctor.

The compensatory character of clinical hypertension cannot be ignored in treatment of the condition. Therapeutics as a science is steadily moving

forward. Through birth of the sister science of Pharmacology, the precise modes and places of drug action have become established, drugs with previously assumed virtues have been discarded and others with unrecognized potentialities have been given a place in therapeutics as a result of pharmacological experimentation. However, *the application of knowledge* gained through pharmacological investigations is still guided too generally by allopathic doctrines. Blood pressures are found to be high, the indications are to administer drugs which pharmacological research assures us will lower it—so runs the allopathic philosophy. A great scientific principle is forgotten, viz, that guidance and treatment can ordinarily accomplish no greater good than to assist the compensatory or curative processes that are naturally called into play. Certainly any remedy or agent that thwarts the natural compensatory processes should be employed only advisedly.

The question may now be raised whether it is advisable to lower blood pressures in hypertension unless real dangers appear to be impending. S. Weiss and Ellis justly warn that "therapeutic procedures which lower blood pressure through decreased cardiac output can only be harmful." But the indiscriminate use of vasodilating drugs is equally undesirable. Their effect on blood flow through an organ is always the resultant of two actions, viz, the local change in caliber of vessels and the degree to which pressure is lowered in the aorta. Now it is a fact that vasodilator drugs without exception act predominantly on those arterioles that possess the great-

est number of muscle fibers. For example, they affect vessels of abdominal organs more than vessels of the heart and brain, hence the flow through the latter is determined by the change in aortic pressure rather than by local variations in caliber. I have repeatedly demonstrated experimentally, for example, that amyl nitrite, contrary to general belief, reduces bloodflow through the coronary and cerebral vessels.

Obviously such lowering of blood pressure defeats the purpose of natural compensatory mechanisms, and at times may actually be dangerous. An experimental observation may be added to emphasize this statement. When the abdominal aorta of a dog is occluded for an hour or more and the compression then released, aortic pressures fall to very low levels and the animal soon dies of circulatory failure. Erlanger attributed these reactions to shock resulting from prolonged anoxemia of tissues, but my own evidence shows convincingly that the marked fall of pressure is directly due to myocardial failure. Venous pressure rises, it does not fall as in shock, the small cardiac ejections are due to impaired contraction, not to deficient filling as in shock. The reduced coronary flow following the sudden decrease in aortic pressure after decompression is undoubtedly the factor that initiates the myocardial failure. Little imagination is required to suggest how much more serious a sudden decrease of aortic pressure might be if coronary vessels are sclerosed in addition.

There can be no doubt that the patient with great hypertension is confronted with certain risks, such as rup-

ture of blood vessels or decompensation of the heart. But physiological considerations suggest that in attempting to avoid these dangers the wise

physician will consider carefully whether an even greater risk is not incurred through the use of drugs which lower systemic pressures generally.

BIBLIOGRAPHY

Arterial Elasticity and Pulse Velocity

BAZETT, H C and DRYER, N B Measurements of pulse wave velocity, *Am Jr Physiol*, 1922, lxi, 94-116

BRAMWELL, J C Arterial elasticity in man, *Quart Jr Med*, 1924, xvii, 225-243

BRAMWELL, J C and HILL, A V The velocity of the pulse wave in man, *Proc Roy Soc*, 1922, xciii, Series B, 229-306
Velocity of transmission of pulse-wave and elasticity of arteries, *Lancet*, 1922, i, 891-892

BRAMWELL, J C, McDOWALL, R J S, and McSWINEY, B A The variation of the arterial elasticity with blood pressure in man, *Proc Roy Soc*, 1922-23, xciv, Series B, 450-454

BRAMWELL, J C, McDOWALL, R J S, and McSWINEY, B A The velocity of the pulse wave in man in relation to age as measured by the hot-wire sphygmograph, *Heart*, 1921-23, ix-x, 237-249

BRAMWELL, J C, DOWNING, A C, and HILL, A V The effect of blood pressure on the extensibility of the human artery, *Heart*, 1921-23, ix-x, 289-300

ERLANGER, J, and HOOKER, D R An experimental study of blood pressure and of pulse pressure in man, *Johns Hopkins Hosp Rep*, 1904, xii, 145-378

FRANK, O Die Elastizität der Blutgefäße, *Ztschr f Biol*, 1920, lxxi-ii, 255-272, 1928, lxxviii, 105-118

FRANK, O Das Altern der Arterien, *Sitzungs d Gesellsch f Morphol u Physiol in Munch*, 1927, xxxii, 23-32 (Abstract in *Ber u d Gesamte Biol Abt b Physiologie*, 1927, xli, 234-235)

FRIBERGER, R Über die Pulswellengeschwindigkeit bei Arterien mit fühlbarer Wandverdickung, *Deutsch Arch f klin Med*, 1912, xcvi, 280-295

HEMINGWAY, A, McSWINEY, B A, and ALLISON, P R Extensibility of hu-

man arteries, *Quart Jr Med*, 1928, xxi, 489-498

LYON, D M, and SANDS, J Studies in pulse wave velocity IV Effect of adrenalin on pulse wave velocity, *Am Jr Physiol*, 1924, lxxi, 534-542

LAUBRY, C H, MOUGEOT, A, et GIROUX, R La vitesse de propagation de l'onde pulsatile artérielle, *Arch d mal du coeur*, 1924, xiv, 49-70

Hypotension artérielle, *Arch d mal du coeur*, 1924, xiv, 97-129

MACWILLIAM, *Proc Roy Soc*, 1902, lxx, 107

MUNZER, E Die Fortpflanzungsgeschwindigkeit der Pulswellen in gesunden und krankhaften, veränderten Blutgefäßen, *Verhandl d Kongresses f inn Med*, 1912, xxix, 431-443

ROY, C S The elastic properties of the arterial wall, *Jr Physiol*, 1880-1, iii, 125-129

SANDS, J Studies in pulse velocity, pulse wave velocity in pathological conditions, *Am Jr Physiol*, 1925, lxxi, 519-533

STRASBURGER, J Über den Einfluss der Aortenelastizität auf das Verhältnis zwischen Pulsdruck und Schlagvolumen des Herzens, *Deutsch Arch f klin Med*, 1907, xci, 378-427

Mechanisms Producing Peripheral Resistance Increase

GAGER, L T Hypertension 1931, Williams and Wilkins Company, Baltimore
HERING, H C Arterieller Hochdruck und Arteriolen-Veränderung, *Ztschr f Kreislaufforsch*, 1930, vii, 231-236

HOCHREIN, M Habilitationsschrift, 1928 Vogel, Leipzig

KOCH, E, MIES, H, and NORDMANN, M Arterieller Hochdruck durch Dauerschaltung der Blutdruckregler, *Ztschr f Kreislaufforsch*, 1927, vi, 585-600

NORDMANN Über Aortenveränderungen nach Dauerausschaltung der Blutdruckjugler, Munch med Wchnschr., 1928, lxxv, 1658

REGNIERS, P. Le sinus carotidien en clinique, Rev belge sc méd, 1930, ii, 601-622

Experimental Hemodynamics and Cardiodynamics

FAHR, G Work of left ventricle in normal, hypertension and arterio-sclerosis, Proc Soc Exper Biol and Med, 1927, xxiv, 405-410

FAHR, G, and DAVIS, J Effect of general systemic arteriosclerosis upon heart and systemic circulation, Ann Int. Med, 1930, iv 211-216

FAHR, G, DAVIS, J C, and SPITTLER, R Hemodynamics of arteriosclerosis, influence of elastic factor on circulation, Proc Exper Biol and Med, 1929-30, xxvii, 325-327, Am Jr Physiol, 1931, xcvi, 426-438

HOLMAN, E, and BECK, C S The physiological response of the circulatory system to experimental alterations, Jr Exper Med, 1925, xlii, 661-692

KATZ, L N Observations on the external work of the isolated turtle heart, Am Jr Physiol, 1922, xcix, 579-597

STARLING, E H, and VISSCHER, M B The regulation of the energy output of the heart, Jr Physiol, 1926-27, lxi, 243-261

WIGGERS, C J Modern aspects of the circulation in health and disease, 1923,

Lea and Febiger, Phil and N Y. The pressure pulses in the cardiovascular system, 1928, Longmans, Green and Company, London

WIGGERS, C J and KATZ, L N Static and dynamic effort of heart during ejection, Am Jr Physiol, 1928, lxxv, 229-250

Physiology of Clinical Hypertension

BURWILL, C S, and SMITH, N C. Output of heart in patient with abnormal blood pressures, Jr Clin Invest, 1929, vii, 1-10.

ERNST, C, and WEISS, R Über das zirkulatorische Minutenvolumen bei der Hypertonie, Ztschr f d ges exper. Med, 1929, lxxvii, 126-138

FEIL, H S, and KATZ, L N: Clinical observations on the dynamics of ventricular systole II Hypertension, Arch Int Med, 1924, xxxiii, 321-329

HOCHREIN, M Habilitationsschrift, 1928, Vogel, Leipzig

Über den Kreislaufmechanismus bei der Hypertension, Arch f exper Path u Pharmacol, 1928, cxxxiii-cxxxiv, 325-384

LAUTER, S, und BAUMANN, H Über den Kreislauf bei Hochdruck, Arteriosklerose und Apoplexie, Ztschr f klin Med, 1928, cix, 415-446

WEISS, S, and ELLIS, L B Quantitative aspects and dynamics of circulatory mechanism in arterial hypertension, Am Heart Jr, 1930, v, 448-468

Essential (Primary) Hypertension: A Clinical and Morphological Study of 375 Cases*†

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THE variety of symptoms and vascular lesions associated with essential hypertension is so great that consecutive stages of the disorder may appear at times to be diseases of different kinds. Most cases of essential hypertension conform to the usually well recognized course of chronic hypertension which terminates, after years, in heart failure, cerebral hemorrhage, renal failure or some intercurrent infection. But there is a small group of cases, which, because of the peculiarities of the symptoms and vascular lesions, has been set aside by some observers in a separate class and designated "malignant" hypertension. Over the pathogenesis of the arteriolar lesions in this group, especially in the kidney, considerable controversy has arisen.

As early as 1910 Volhard and Fahr¹ differentiated the red granular kidney

from the genuine contracted kidney leading to renal insufficiency. They² later clearly distinguished two forms of essential hypertension (a) the benign form characterized by arteriosclerosis of the small renal arteries and (b) the malignant form or the combination form distinguished by the addition of an inflammatory factor to the kidney already damaged by arteriosclerosis. Although there has been objection to the use of the terms benign and malignant in connection with cases of hypertension, they have become so well established in the literature that it is difficult to discuss hypertension without referring to them. The division of cases of hypertension into benign and malignant forms is convenient. But it must be recognized that benign cases may end fatally in uremia, the benign case may become transformed into the malignant one; there may be intermediate cases having features of the benign type with a few of the characteristics of the malignant form, and finally that there may be degrees of intensity of the symptoms and vascular lesions within the malignant group.

In this report an analysis is presented of the clinical and postmortem

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data obtained from a study of 375 cases of primary (essential) hypertension. An attempt is made to show that the varieties of clinical and morphological changes observed are manifestations of the different stages of one process. In order to obviate the impression that the cases with an intense and rapid course may be considered as a separate condition, and to emphasize the unity of the clinical and morphological features, all cases are divided into three groups corresponding to three consecutive stages of the disease. This grouping is unimportant except that it is of immediate convenience. Cases of early hypertension in which symptoms appear to be independent of the vascular lesions are placed in group 1, this may be called the functional stage.

In group 2 are the cases in which hypertension is associated with definite arteriosclerosis slowly progressing to the breakdown of essential organs; this may be designated the arteriosclerotic stage. And finally, in group 3, are the cases of so-called malignant hypertension. Corresponding to the stormy clinical course are the necrotic lesions in the arterioles of the kidney and other organs; hence the term arteriolonecrotic stage may be appropriate for this group.

MATERIAL STUDIED

For the purpose of this report cases were included in which there was a persistent systolic blood pressure of 160 mm of mercury or above, and a diastolic pressure of above 100 mm of

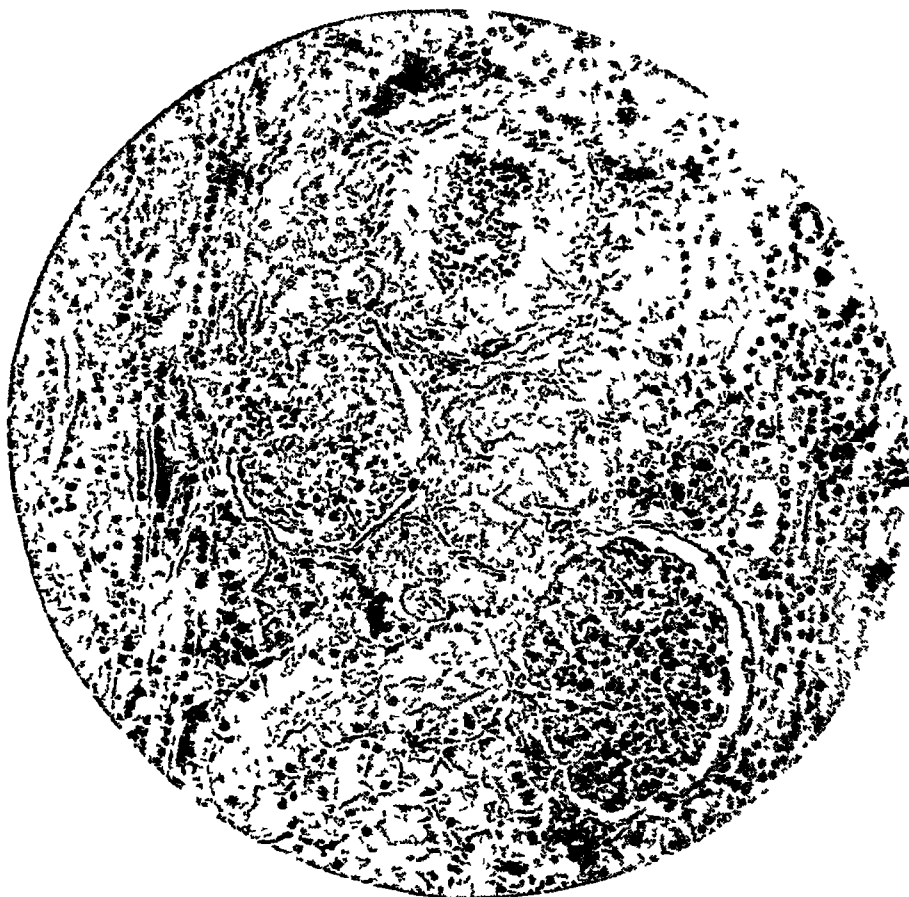


FIG 1 (Group 1) Normal glomeruli and arteries seen in group 1

mercury Cases of glomerular nephritis, toxemia of pregnancy, hyperthyroidism and aortic regurgitation were excluded, as well as any other case in which the cause of the hypertension was apparent

Hypertension, without clinical evidences of arteriosclerosis other than those seen in normal people, was the chief feature of cases in group 1 There were no symptoms or signs ordinarily present in cardio-vascular-renal disease Symptomatically a vasomotor derangement of the type often seen in neurasthenia was the essential change Frequently there were no symptoms Patients died of causes independent of cardio-vascular-renal changes, an accident, an operation, or an intercurrent infection was the chief cause of death There were 43 cases in group 1 In group 2 the cases are recognized as those having arteriosclerosis of peripheral as well as internal arteries This group represents a stage of slow progression and the symptoms are those produced by arteriosclerotic narrowing of the lumina of arteries leading to ischemia and slow fibrosis of internal organs Heart failure, cerebral acci-

dent, renal failure and thrombosis may appear in this stage There were 303 cases in group 2 The remaining 29 cases were placed in group 3 Clinically the patients of the last group had the following distinctive features a) persistent excessive hypertension, b) violent headaches, c) rapid progressively downward course, d) sudden loss of weight and strength, e) typical retinal changes, f) a course resistant to treatment, and g) a termination with a functional breakdown of some essential organ, usually the kidney or the heart Histologically there was an advanced severe diffuse arteriosclerosis with necrotic lesions of the arterioles of various organs A detailed analysis of the clinical and histological features of 12 of the 29 cases included in group 3 was reported previously by Murphy and Grill³

ANALYSIS OF CLINICAL DATA

The causes of death in this series as well as the number and percentage of each are arranged in five groups as shown in table 1 Heart disease caused death in 188, or 50 per cent of all cases It is seen that 171, or

TABLE 1
CAUSES OF DEATH IN 375 AUTOPSIED CASES OF ESSENTIAL HYPERTENSION

	GROUP I		GROUP II		GROUP III		TOTAL	
	NO	PER CENT	NO	PER CENT	NO	PER CENT	NO	PER CENT
1 HEART DISEASE	10	23.3	171	56.4	7	24.1	188	50.0
2 RENAL FAILURE	0	0	23	7.6	16	55.2	39	10.4
3 APOPLEXY OR THROMBOSIS AND EMBOLISM	0	0	45	14.9	5	17.2	50	13.4
4 INFECTIONS	12	27.9	40	13.2	1	3.5	53	14.2
5 MISCELLANEOUS	21	48.8	24	7.9	0	0	45	12.0
TOTAL	43	100.0	303	100.0	29	100.0	375	100.0

56.4 per cent of cases, in group 2 died of heart disease while in group 3 only 7, or 24.1 per cent, had heart failure. Ten patients, or 23.3 per cent, of group 1 died of heart disease but usually of a type produced by infections and not hypertension. In sharp contrast to the percentage of deaths caused by heart disease was the low mortality rate from renal failure. Thirty-nine only, or 10.4 per cent, died from renal failure. Of these 23, or 7.6 per cent, occurred among cases of group 2, 16, or 55.2 per cent, among those of group 3. In group 2 uremia followed a slowly progressing renal failure, but in group 3 uremia developed suddenly and caused early and rapid death. It was unexpected to find that only 45, or 14.9 per cent, of the patients in group 2 died of cerebral hemorrhage or thrombosis, while in group 3 five deaths from apoplexy, or 17.2 per cent, were not exceptional. Of the infections which caused death in 53 cases, or 14.2 per cent, pneumonia was the most prominent. Erysipelas and gangrene of the feet occasionally occurred.

The ages of the patients ranged from 9 to 100 years. They are arranged ac-

cording to decades and the number and per cent in each group are given in table 2. In group 3 (malignant), 62.3 per cent of the individuals were under 50 years of age; while in groups 1 and 2 (benign), 16.3 per cent were under 50 years of age. In order to emphasize this interesting comparison the age incidence was arranged as shown in table 3. The occurrence of so many patients of advanced years may be explained by the fact that many of the patients were inmates of a county infirmary.

Throughout the three stages there were two unifying clinical factors, hypertension and left ventricular hypertrophy. The length of time elapsing between the onset of hypertension and the occurrence of other symptoms was unknown in most cases. However, in some cases it is known that as short a time as one year, and in other cases as long as 15 years, elapsed before the usual symptoms developed. The degree of hypertension in groups 1 and 2 varied considerably, fluctuating in some cases between 150 mm and 300 mm. of mercury systolic, and from 100 mm to 160 mm. of mercury dias-

TABLE 2
AGE INCIDENCE IN 375 AUTOPSIED CASES OF ESSENTIAL HYPERTENSION

AGE	GROUP I		GROUP II		GROUP III		TOTAL	
	NO	PER CENT	NO	PER CENT	NO	PER CENT	NO	PER CENT
10-20	0	0	0	0	3	10.4	3	0.8
21-40	9	21.0	8	2.64	7	24.1	24	6.4
41-60	23	53.5	65	21.5	15	51.7	103	27.3
61-80	10	23.2	166	54.8	4	13.8	180	48.1
81-100	0	0	35	11.5	0	0	35	9.4
UNKNOWN	1	2.3	29	9.6	0	0	30	8.0
TOTAL	43	100.0	303	100.0	29	100.0	375	100.0

TABLE 3

A COMPARISON OF AGES OF PATIENTS IN GROUPS 1, 2, AND 3

AGE	(BENIGN) GROUPS 1 AND 2	(MALIGNANT) GROUP 3
0-10	0	1
11-20	1	2
21-30	3	2
31-40	12	6
41-50	36	7
51-60	56	7
61-70	100	4
71-80	80	0
81-100	30	0
TOTAL	318	29

tolic In group 3 this changeableness was less noticeable. The accompanying symptoms appeared to bear no relation to the height of the blood pressure in any group. In group 2 a few patients were observed who showed systolic pressures above 200 mm of mercury and independent of treatment had normal pressures with no heart failure within a period of one year. Of the 303 cases in group 2, 32 or 10.5 per cent had no hypertension during the last period of observation preceding death. Previous records in some of the cases proved hypertension to have been present on former observations. In other cases, evidences such as cardiac hypertrophy, retinal and peripheral arteriosclerosis, as well as arteriosclerosis of the smaller arteries in the kidney were taken as proof of a pre-existing hypertension. Obviously the blood pressure dropped in many cases of coronary disease and myocardial failure.

Left ventricular hypertrophy was present at autopsy in 263, or 79.4 per cent, of all cases, there was no record in 44 and in 68 cases no enlargement was present. Of the 263 cases of proved left ventricular hypertrophy, only 182 were recognized clinically, in-

dicating a considerable disparity between the clinical and postmortem figures. The two chief clinical manifestations of heart disease were angina pectoris and the syndrome of left ventricular failure. The frequency of angina pectoris was difficult to determine because patients were frequently unable to distinguish between pain in the cardiac area and other sensations often produced by left-sided heart failure, such as constriction, heaviness, distension, and suffocation in the sternal region. It was estimated that 42, or 11.2 per cent, of the 375 patients had angina pectoris. Pain in the heart area was the first symptom of heart disease in approximately 18, or 5 per cent, of all patients having heart failure. The syndrome of left ventricular failure was the outstanding feature. Of the 188 patients dying of heart disease it was the first evidence of any disorder noted by the patient in 105, or 55.8 per cent. This classical syndrome developed in every case of heart failure from hypertension. It was characterized by paroxysmal dyspnea usually worse at night, palpitation of the heart, and a sense of distress in the heart area. Dyspnea, usually nocturnal at first, was the earliest symp-

tom of heart failure in most cases although attacks of dyspnea varied in time and duration; as a rule, they persisted for about twenty minutes in the earlier stages and then subsided only to return about the same time the following night. Frequently patients worked during the day without experiencing recurrent attacks. After some weeks or at times months, attacks came during the day and recurred so frequently that the patient was confined to bed. With the onset of this type of dyspnea, the outlook for the patient was distinctly bad, a few patients, however, recovered and lived only to die of heart failure or apoplexy in later years. Palpitation, although frequently present,

was the first symptom in only a few cases.

Murmurs were most frequently heard at the mitral area, being recorded in 85 cases, or 22.6 per cent of all cases. Aortic systolic murmurs were less common, being noted in 52, or 13.8 per cent of cases. A soft diastolic aortic murmur transmitted down the left sternal border was occasionally found. Of greater importance than murmurs was the frequent presence of a gallop rhythm. It was noted in 95, or 50.5 per cent, of the 188 cases of heart failure. Usually the onset of gallop rhythm indicated a progressive left ventricular failure. A few exceptions to this rule were observed.

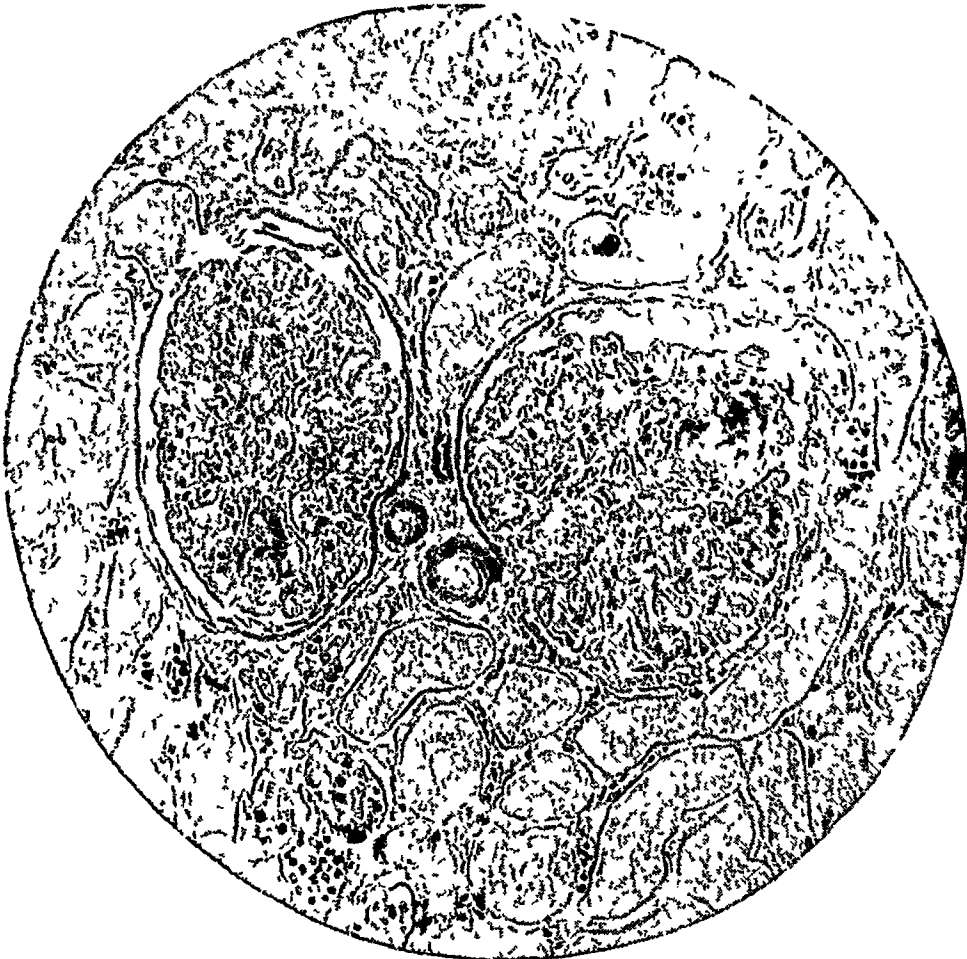


FIG 2 (Group 2) Focal thickening of the capillary basement membrane with mild arteriosclerosis. Azo-carmin stain.

Electrocardiographic examinations revealed a variety of changes. The most common were left ventricular preponderance and evidences of left bundle branch block, many were normal.

Although an arteriosclerotic contracted kidney was commonly found at autopsy, uremia was a rare complication, occurring in only 39, or 10.4 per cent, of all cases.

Clinically the following renal functional tests were used routinely in all cases. (a) phenolsulphonphthalein test, (b) urea concentration test of McLean, (c) dilution and concentration tests of Volhard, (d) blood nitrogen estimations weekly, (e) the urea clearance test was used to some extent during the past two years and was found to be the most satisfactory one in giving information of early renal failure. In group 3 the kidney destruction from the necrotic and thrombotic complications of the arteriosclerosis was associated with sudden and early uremia, while in group 2 the ischemic atrophy of the kidney was a slower process taking months and years completely to render the kidneys insufficient. Albuminuria was a constant feature of cases in both groups having renal failure. There was, however, a difference in the response to treatment of the renal failure in the two groups, renal failure in group 3 was decidedly resistant to treatment while that in group 2 frequently appeared to be benefited by treatment. Frequently albumin was found independent of casts, red blood cells and pus cells. In such cases the albuminuria was assumed to be caused by renal congestion from a failing heart.

The presence of small quantities of albumin associated with many red cells and pus cells was considered to be evidence of small infarcts due to arteriosclerotic occlusion of smaller arteries. Heavy albuminuria with casts, red cells and pus cells was found with renal failure in both groups 2 and 3. Extrarenal factors, such as heart failure and infections added to kidneys already damaged by arteriosclerosis, occasionally caused renal failure. Edema of the nephritic type did not occur in this series. There was no hypercholesterolemia present and doubly refracting lipoids were not found in the urine of patients suffering from edema. The albumin and globulin content of the blood was always normal in cases in which estimations were done. Edema, when present, was of the cardiac variety. Although pallor of the skin was noticeable in many cases, anemia was infrequent except in cases of renal failure when it was observed in some but not all cases.

Apoplexy was the cause of death in 50, or 13.4 per cent, of the cases. Hemorrhage in other parts of the body was occasionally observed. There were two cases of renal hemorrhage, one case had hemoptysis and autopsy revealed no pulmonary tuberculosis or any disease aside from arteriosclerosis. Hematemesis was observed once in this series. Epistaxis was more frequent. Vascular crises producing transient hemiplegia or aphasia with monoplegia were observed four times. In a few cases in group 3 there were periodic attacks of abdominal cramps and of severe headache. Such attacks were believed to be caused by vascular crises involving visceral arteries of the ab-

domen and of the brain respectively. These periodic attacks remained for periods varying from several hours to several days. There were two patients belonging to group 3 who developed hemorrhages into the skin resembling purpura hemorrhagica. The lesions varied in size from several millimeters to large blotches of several centimeters in diameter. The disease in both instances progressed rapidly to a fatal termination.

RETINAL CHANGES

Recent work done in this country chiefly by O'Hare and Walker,⁴ Keith, Wagener and Kernohan⁵, Fishberg and Oppenheimer,⁶ and Wagener,⁷ has established the relationship between the various stages of hypertension and the changes in the arterioles of the retina. In accordance with other observers we have found the vascular changes in the retina one of the best indicators of the degree of vascular changes throughout the body. For the purpose of prognosis the retinal lesions in group 3 are of considerable importance.

In the cases of early essential hypertension (group 1) the retinal examinations revealed no abnormalities. In cases of longer duration, evidences of arteriosclerosis were usually present. Narrowing of the arterioles with increase of the light-reflex of the arteries, tortuosity of the arteries and arteriovenous compression were the usual features. Occasionally, there were small hemorrhages along the course of some vessels and at times white patches were seen produced probably by an old healed hemorrhagic area. The disks in this group were clear and edema of the retina was

mild. By observing these eye changes from time to time the rate of progress of arteriosclerosis may be determined. Usually the retinal arteriosclerosis in group 2 was a slowly changing process corresponding in general with the vascular changes in the kidney and in other organs of the body. The lack of destructive changes in the disks was in sharp contrast with the lesions seen in the more advanced cases of group 3 (malignant). The changes in the eye grounds in group 3 were more characteristic than in group 2. Obviously, since the vascular lesions of groups 2 and 3 are only different stages of one process, cases were seen in which the changes in the eye were of the transitional form corresponding to the type termed by Wagener⁷ retinitis of severe benign hypertension. Lesions of the fundi were always found in group 3 and were characterized by papilledema, hyperemia of the disks, and constriction of the arterioles leading to the appearance of thin white lines buried in the retinal edema. Hemorrhages along the course of the arteries were frequently found. White patches were seen which corresponded to what has been designated "cotton wool" patches. These patches seemed fresher and had irregular borders that appeared to merge with the generalized edema of the retina. They lacked the clearcut glistening features of those white patches seen in the cases of group 2. In three cases in group 3 a previous diagnosis of brain tumor was made upon the changes of the eye grounds. In two of our cases in group 3, the characteristic lesions in the fundus were present before any evidence of renal damage occurred. Al-

buminuria and renal failure developed within the first few months of observation. One case in group 3 was noted in which the advanced changes in the eye grounds were absent. There was no abnormality except a mild arteriosclerosis of the retinal arteries and yet the patient died of uremia. Histologically the kidneys showed the typical arteriolonecrotic lesions seen in malignant nephrosclerosis of Fahr. When the typical retinal changes are found in the absence of renal and heart failure it is fairly certain that breakdown of the organism will follow within a period of several months. That onset of renal failure does not influence markedly the retinal picture is concluded from a study of our cases of renal arteriosclerosis with gradual renal failure in group 2. Of the 23 cases of ischemic atrophy of the kidney leading to renal insufficiency, eight were examined ophthalmoscopically. No changes were observed other than a simple arteriosclerosis. We found that the retinal vascular changes are a fair index of the lesions progressing in other organs of the body. For the purpose of exact diagnosis and prognosis

ophthalmoscopy is of no little importance.

ANALYSIS OF PATHOLOGICAL DATA

Postmortem examinations were made in all the cases. All sections were studied with hematoxylin and eosin, Van Gieson's and Weigert elastic tissue stains and Sudan III. Selected cases were studied with modified Heidenhain-Mallory stain. When fat was present polariscopic examinations were made for doubly refracting lipoids. Corresponding to the clinical groups representing successive stages of the disease, three stages of arteriosclerosis were recognized. Mild arteriosclerosis involving chiefly larger and medium sized arteries of organs such as the kidney, liver and spleen was the main feature of group 1. A more advanced arteriosclerosis of the smaller as well as the larger arteries of kidneys and other organs characterized group 2. The essential change in group 3 (malignant) was an intense diffuse arteriosclerosis extending into the smallest arteries and arterioles and producing at times an arteriolonecrosis.

As shown in table 4, cardiac hyper-

TABLE 4
HEART WEIGHTS IN 375 CASES OF ESSENTIAL HYPERTENSION

HEART WEIGHTS	GROUP 1		GROUP 2		GROUP 3		TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
NORMAL WEIGHT	18	41.85	50	16.5	0	0	68	18.13
400- 600 GMS	14	32.55	151	49.84	14	48.27	179	47.74
600- 800 GMS	7	16.3	51	16.83	9	31.03	67	17.87
800-1000 GMS	0	0	14	4.62	3	10.35	17	4.53
NOT RECORDED	4	9.3	37	12.21	3	10.35	44	11.73
TOTAL	43	100.00	303	100.00	29	100.00	375	100.00

trophy was found in 263, or 79.4 per cent, of 331 hearts examined; in 44 no record was made. Slight left ventricular hypertrophy was noted in group 1; 21 of 39 hearts were above normal weight. Of 266 in group 2, 216, or 81 per cent, were hypertrophied, while in group 3 hypertrophy was present in every case recorded. Coronary disease, characterized grossly by occlusion of a large branch of the artery from thrombosis or a decided narrowing due to arteriosclerosis was recorded in 44, or 25.7 per cent, of 171 cases examined in group 2. In these cases myocardial infarcts or scars and diffuse fibrosis of the heart muscle were present. Oc-

asionally a diffuse fibrosis and scars were present when the coronary disease seemed insufficient to cause any trouble. In 4 cases the left ventricle was considerably hypertrophied and dilated and little or no fibrosis or coronary disease was found. Death was due in each case to left ventricular failure. In no case in group 3 was there macroscopic evidence of complete coronary occlusion, although coronary sclerosis with narrowing was always found. Arteriosclerotic lesions of the aortic valves leading to deformities and insufficiency were occasionally observed. Less often, the mitral valve was involved in the arteriosclerotic

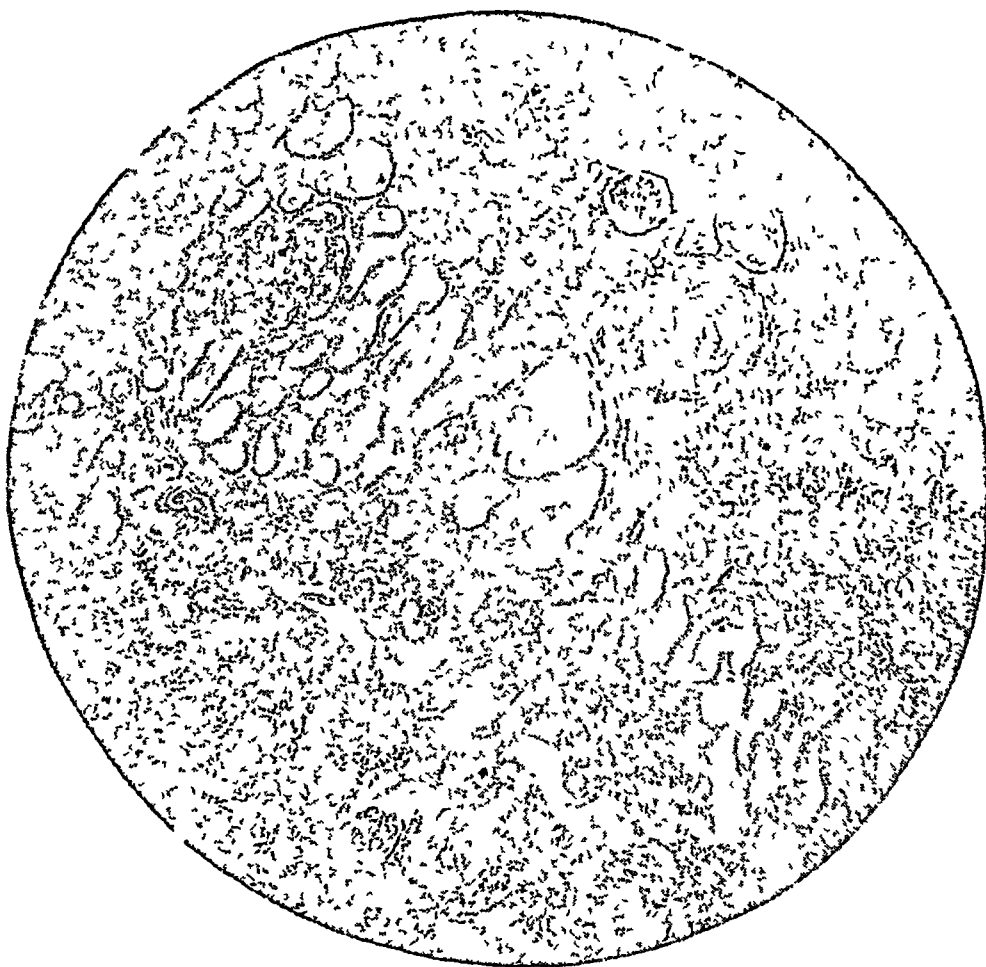


FIG 3 (Group 3) Section showing the increase in the stroma, the dilated tubules, the sparsity of the glomeruli, and the extensive arteriosclerosis of the smallest arteries

process The arterioles of the myocardium were usually normal

The size and appearance of the kidneys were decidedly variable Some kidneys were shrunken and granular, others were large and smooth Microscopically arteriosclerosis of the small arteries of the kidney was constantly found In some cases it was widespread, in others, it had a focal distribution Variations in size, color and surface markings did not conform to any stage of the disease Kidney weights were available in 267 cases The average weight in 33 cases of group 1 was 181.5 gm, of the right, 176 gm, and of the left, 187 gm In group 2, the average weight of kidneys in 205 cases was 133.5 gms, of the right, 129, and of the left, 138 gm The largest kidney weighed 280 and the smallest 90 gms In the 29 cases of group 3 the average weight was 115 gms, of the right kidney, 112, and of the left, 116 gms The smallest kidney weighed 29 gms, the largest, 255 gms In one case there was a congenital absence of the left kidney, the right weighed 255 gms

Kidneys in group 1 were always either normal in size or larger than usual and the surface was smooth Evidences of arteriosclerosis were confined to the larger branches, and yellowish streaks in the intima due to lipid deposits were frequently the only sign of disease Grossly the kidneys in group 2 were of the shrunken granular type The degree of contraction and granulation varied Scattered scars due to healed infarcts were occasionally seen on the surface of an otherwise normal appearing kidney The cortex of the kidneys in both

groups 2 and 3 was narrowed, and especially in group 2, accumulation of fat appeared in the renal pelvis Kidneys of the contracted granular type were usually present in group 3 Occasionally they were larger than normal with a smooth surface or of normal size without granulation Extensive subcortical hemorrhages were present in all but 5 cases Small hemorrhages in the mucosa of the pelvis were constantly found, and in several cases there were blood clots with evidences of larger hemorrhages from the kidney

Microscopically the changes in group 1 were few and were substantially the same as those in non-hypertensive individuals of the same age The arterioles and the smaller portions of the interlobular arteries were normal Occasionally there were areas showing arteriosclerosis of the medium-sized arteries along with foci of hyalinized and fibrosed glomeruli Such lesions were the same as those found in the later stages, except that they were so few in number that they may be looked upon as normal Concerning the size of the glomeruli there was no constancy Most glomeruli were of normal size, some were hypertrophic, and a few were atrophic The tufts undergoing atrophy showed various grades of hyaline and fatty degeneration and fibrosis The glomeruli in many cases were further studied with the Mallory-Heidenhain azo-carmin stain, as suggested by McGregor⁶ All of the cases in group 3 and 141 cases in groups 1 and 2 were examined with this stain In group 1 and in some cases of group 2 representing the earlier stages of arteriosclerosis focal thickening of the

glomerular basement membrane was observed. Thickening and wrinkling of the glomerular basement membrane was noted in some cases where the smallest arteries and arterioles were intact. In more pronounced cases of contracted kidney these changes in the basement membrane were widespread and the glomeruli were more diffusely involved. Although thickening of the glomerular basement membrane was present with contraction of the renal corpuscle in some form in all cases of hypertension, such changes cannot be considered specific for cases of hypertension only, as identical changes in the basement membrane were observed in cases known to have had no hypertension. Similar changes were easy to demonstrate in kidneys of older people where the afferent arterioles as well as smaller arteries were free from arteriosclerotic changes.

In group 2 the arteriosclerosis had advanced to such extent that functional derangement of some internal organ followed ischemia. Of the lesions present in all organs, those in the kidney were found to be the most accurate index of the progress of arteriosclerosis. The predominant lesion was an arteriosclerosis of the larger and medium-sized arteries. In some cases, however, there was an extension of the arteriosclerotic process into the smaller and smallest branches of the interlobular artery. Occasionally the arterioles were involved. However, such changes were distinctly focal in distribution and frequently led to scattered renal scars. Patches of destroyed tufts were seen with corresponding tubules which showed round cell infiltration and in places advanced

fibrosis with scarring. There were many glomeruli which appeared almost twice normal size; at the same time many were shriveled and atrophic. The number of normal glomeruli depended upon the extensiveness of the arteriosclerosis. Capsular thickening was found varying from a slight proliferation of connective tissue to a thick ring of scar tissue which seemed to obliterate the capillary tuft. Associated with this were areas of interstitial fibrosis, round cell infiltration and peri-glomerular fibrosis. Hyaline and fatty degeneration of afferent arterioles with extension of the degeneration into the glomeruli were frequently seen. A distinct feature was the diffuse thickening of the capillary basement membrane. This thickening, in contrast to the earlier stage seen in group 1, was almost universal in many cases. It is obvious that within group 2 there may be a variety of histological changes depending mostly upon the extent and severity of the arteriosclerotic process. Although in groups 1 and 2 the essential histological lesion is an arteriosclerosis, the chief contrasting feature is the degree of involvement of the various organs. In group 2 the arteriosclerotic process is no longer limited to larger and medium sized arteries but in the kidney the process extends at times down to the finest vessels.

The vascular lesions of the kidney described in group 3 (malignant) have some distinguishing features which have led to their separation from the simple arteriosclerotic renal lesions under the term malignant renal sclerosis. The foudroyant destructive lesions of the kidney in group 3 were in sharp

contrast with the benign sclerosis just described. Although the clinical picture in this group was fairly uniform, the histological lesions showed various degrees of degenerative lesions. In some cases necrosis of arterioles with thrombosis of corresponding capillary loops was a frequent change, and in others an extensive severe arteriosclerosis with little or no necrosis dominated the picture. An analysis of the cases in this group suggests that the typical clinical syndrome may precede the onset of necrosis of renal arterioles. Furthermore heart failure, apoplexy, or some other complication may terminate the patient's life before renal

necrosis occurs. The renal artery was arteriosclerotic in all cases. The lumina of the arcuate and interlobular arteries were reduced in diameter in all instances due to arteriosclerosis. In all cases the cortical stroma was increased but the density varied. Focal infiltration with lymphocytes, plasma cells and occasionally polymorphonuclear leucocytes was a feature of all cases. Alteration of the tubules was constantly present. Areas of dilated tubules with low atrophic epithelial cells were adjacent to islands of compressed atrophic tubules surrounded by increased stroma. Fatty and granular degeneration of the epithelial

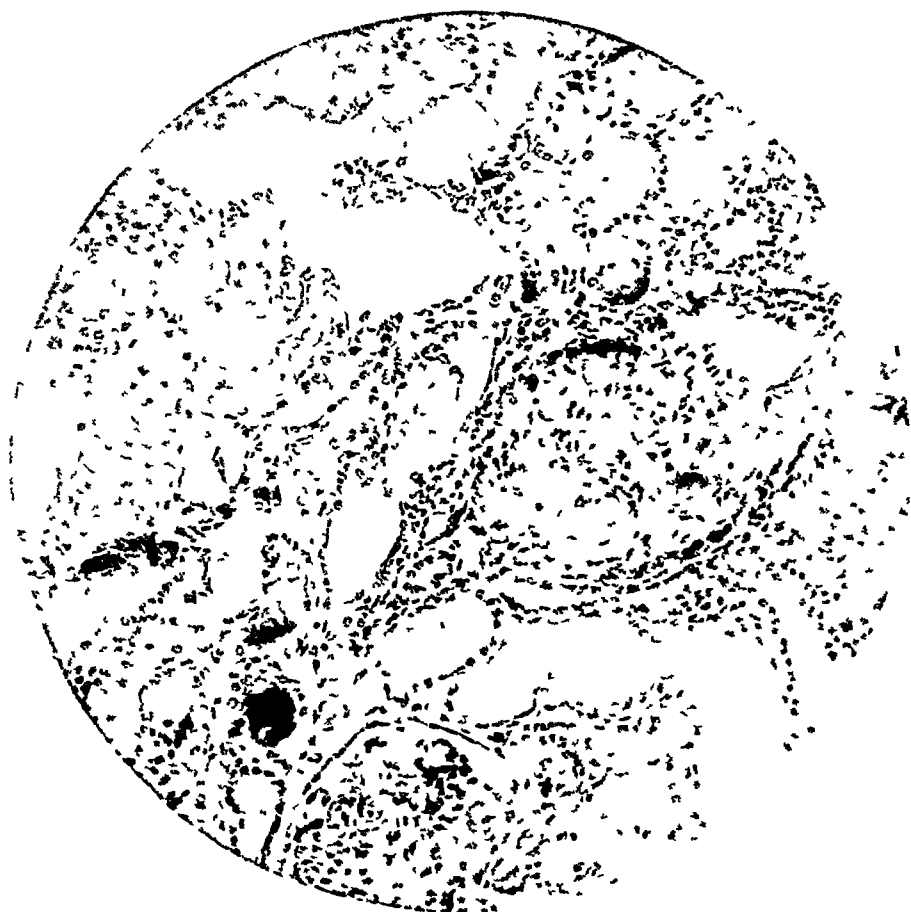


FIG. 4 (Group 3) Arteriolonecrosis with glomerulus illustrating necrosis in capillary loops

cells of the tubules with necrosis in some portions was frequently observed

Damage of the glomeruli was a constant change but the extent of damage varied. Many glomeruli were larger than normal and the capillary loops were normally filled with blood. Others were smaller and more cellular than normal and the loops were bloodless, and again at times the capillary loops appeared to be goiged with red blood cells. The increase in cellularity was caused by an increase in the endothelial and epithelial cells. In some places the capillary loops were adherent to the thickened Bowman's capsules. Thickening of the capsule with desquamation and proliferation of the glomerular and capsular epithelium produced crescents in some glomeruli. In other glomeruli only portions of the loops were involved leaving the remaining part of the tuft normal. Many glomeruli were reduced in size, and fatty and hyaline degeneration of the walls of the loops led to a collapse of the tuft. Hyaline droplet degeneration of the epithelium was frequently demonstrated. There was a widespread and extensive fatty degeneration of the epithelium and capillary endothelium of the glomeruli. The capillary basement membrane of the glomeruli was universally thickened and wrinkled as shown with the aniline-blue stain. In cases where death was caused by apoplexy or heart failure before uremia developed, the glomeruli were usually not so greatly damaged.

The most characteristic microscopic feature was a severe arteriosclerosis attacking the smaller and smallest arteries and arterioles of the kidneys.

The chief distinction was the diffuseness of this process. Elastic hyperplastic thickening of the arteries was present with excessive connective tissue proliferation of the intima of the smaller and smallest arteries. Fatty and hyaline degeneration of the arterioles, and especially the afferent glomerular arterioles, was an outstanding feature. In places fatty and hyaline degeneration occurred with necrosis of the arteriolar wall. In corresponding glomerular loops there was necrosis. Hemorrhagic infiltration of the necrosed arteriolar wall and of the capillary loops was a characteristic feature. The amount of necrosis, however, bore no relation to the degree of renal insufficiency, for in some cases of uremia, necrotic lesions were few and in others with intact function, necroses were numerous. More important was the diffuse intense arteriosclerosis leading to narrowing and obliteration of the lumina of the smallest arteries and arterioles with subsequent ischemia and degenerative changes in the glomeruli. There were degrees of arteriolar destruction depending upon the extent and severity of the necrotic lesions. In some cases necrosis of the arterioles was scarcely found, while in others it was widespread and severe. In one case with widespread arteriolar necrosis and many glomerular infarctions there were areas of perivascular and periglomerular leucocytic infiltration. Aside from this case no such leucocytic infiltration was observed in this series. Scattered throughout the cortex, in many cases, however, nests of leucocytes were observed.

Concerning the changes in the

media of renal arterioles, medial hypertrophy was found occasionally, usually there was atrophy of the media, and at times thickening was due to an increase of connective tissue in the media. Muscular hypertrophy was not a constant nor essential change in this group.

Histological studies were made of other organs including the spleen, lung, pancreas, and liver. In the spleen, liver and pancreas the vascular lesions paralleled those of the kidney quite uniformly. Arteriosclerosis of the smaller and smallest arteries leading to narrowing of the lumina was the chief change. Necrotic lesions were observed outside of the kidney and the eye in only two cases in group 3. In two cases a few necrotic arterioles were seen in the spleen. Pulmonary arteriosclerosis of the smallest arteries and arterioles was a rarity. In three cases there was narrowing of the arteries due to arteriosclerosis.

The arterioles of the skeletal muscle were examined in all cases of group 3 and in 124 cases of groups 1 and 2. The pectoralis major was the muscle usually examined. Hypertrophy of the media of the arterioles was constantly found in group 3. The degree of hypertrophy varied. In some cases it was so decided that the lumen of the vessel was almost closed, in others hypertrophy was slight. Moderate to advanced hypertrophy of the media of arterioles was also observed in 57 cases of group 2. Occasionally proliferation of the intima was observed in these cases.

Microscopic examination of the eye was made in two cases. The walls of the central arteries were thickened,

and the lumina of the branches, especially the arterioles, were decidedly narrowed and occasionally totally obliterated. The choroidal arterioles were variously altered, areas of fatty degeneration and of necroses were seen. In places there was a mild leucocytic infiltration of the necrotic area. The retina was edematous and many hemorrhages were seen especially in the posterior part. No degenerative changes were seen in the arterioles of the extrinsic muscles, but the media was hypertrophied. The optic nerve was edematous and there was an inflammatory exudate composed of lymphocytes and plasma cells.

DISCUSSION

The relationship of the three groups of cases of essential hypertension described here is shown by the presence of such unifying factors as hypertension, cardiac hypertrophy and arteriosclerosis, especially of the renal arteries and arterioles. Clinically and histologically the wide variety of symptoms and lesions encountered was dependent upon several factors. Chief among them was the location of the arteriosclerotic process leading to narrowing and frequently obliteration of the lumina of arteries followed by ischemia and failure of essential organs. In addition to the degree of intensity and extent of the arteriosclerosis, the speed of development of the arteriosclerotic lesions played an important part in determining the changes described. There appeared to be no constant relationship between the height of the blood pressure and the rate of progress or extensiveness of the arteriosclerosis. In some cases

there were no symptoms in the presence of extraordinarily high pressures over a period of years. Undoubtedly hypertension is an important influence in the production of arteriosclerosis, yet the inherent quality of the arteries themselves, and especially their ability to withstand strain, seems to be a more important factor. Since this paper deals only with fatal cases, obviously the study of group 1 is incomplete. Death occurred independently of the hypertension and associated vascular disorders. Ill-defined complaints or a total absence of symptoms characterized this group clinically. Histologically arteriosclerotic changes were few

and were no more extensive than those seen in non-hypertensive individuals of the same age. No case was observed in which there was no renal arteriosclerosis; but in some cases it was limited to the larger and medium sized arteries. In the succeeding stages smaller and smallest arteries were damaged. The vagueness of the symptoms in early hypertension has been emphasized by Allbutt⁹ and Mahomed.¹⁰ Moschowitz¹¹, too, pointed out the significance of the psychic makeup of individuals with essential hypertension. More recently Ayman and Pratt¹², Davis¹³, Riseman and Weiss¹⁴, and Rolleston¹⁵ have reported

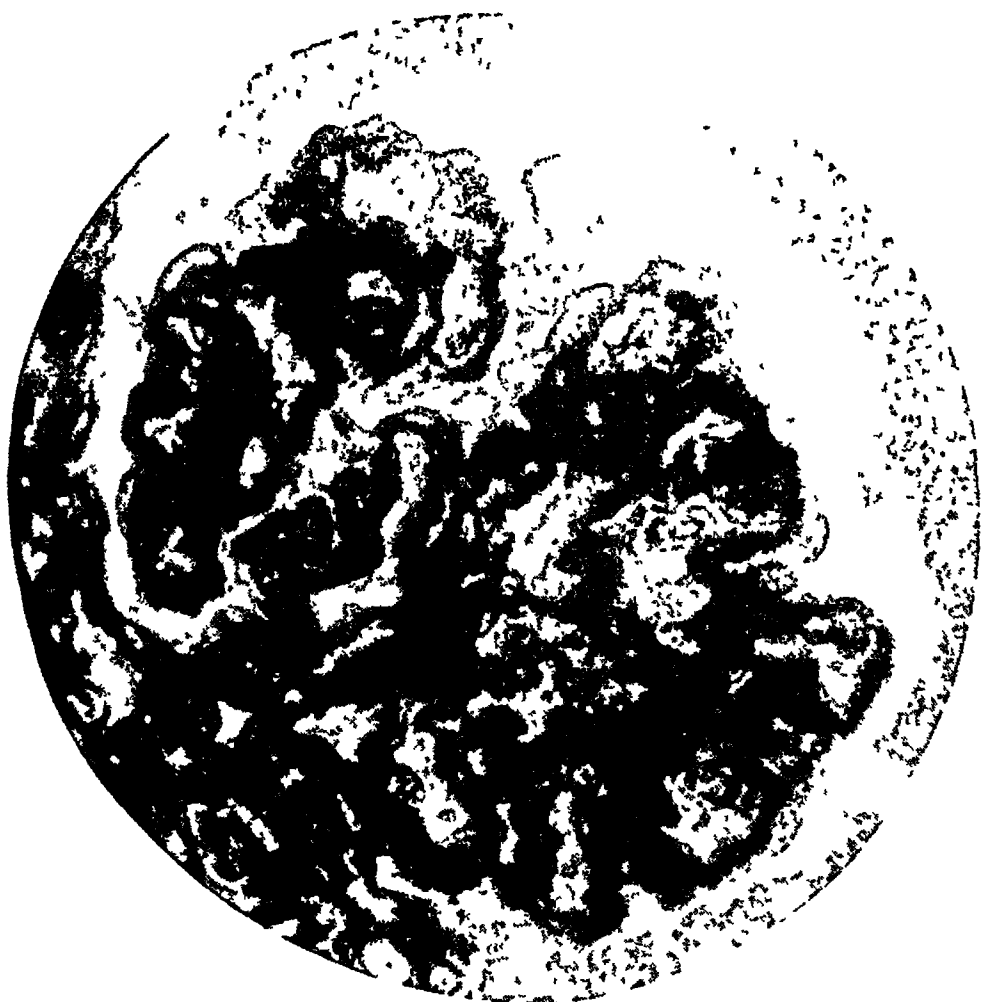


FIG 5. (Group 3) A glomerulus showing the decided thickening and wrinkling of the capillary basement membrane, typical of glomeruli in group 3. Azo-carmin stain

upon the symptomatology of many cases studied in the early stages. All of these investigators observed a parallelism between the early symptoms of essential hypertension and psychic states as seen in psychoneurotics. As emphasized by Fishberg¹⁶, it is unusual to have a case of essential hypertension come to autopsy before hypertension has done any damage to renal arteries. He did, however, study two such cases.

Apoplexy, heart failure and renal failure were the chief complications observed in groups 2 and 3. As shown in Table 1, apoplexy was the cause of death in 50, or 13.4 per cent of cases. These figures are at variance with those of Herxheimer and Schulz¹⁷ who reported that 179, or 44 per cent, of 403 cases had apoplexy. Bell and Clawson¹⁸ found apoplexy in 81, or 19 per cent, of 420 cases. The low figures in our series may be explained by the fact that we included only the primary cause of death in the analysis. For illustration, a patient may have had a cerebral hemorrhage but may have died of uremia. A comparison of the analyses of the data on the heart in groups 2 and 3 reveals that coronary thrombosis or occlusion was an important cause of death in group 2, while it was unimportant in group 3. Of 171 hearts examined at autopsy in group 2, 44, or 25.7 per cent, had coronary occlusion of sufficient extent to damage the heart and cause heart failure, or a coronary thrombosis with a cardiac infarction. Obviously coronary arteriosclerosis was more common than these figures suggest, but only the cases are included in which the coronary disease was advanced enough to produce definite heart disease and

failure. Recently Shapiro¹⁹ reported causes of death in 171 cases of nephrosclerosis. In 16 cases (9 per cent) the cause of death was coronary accident. Of 394 cases of essential hypertension studied at autopsy by Herxheimer and Schulz¹⁷ cardiac hypertrophy was present in 384 cases, or 97.5 per cent. Bell and Clawson¹⁸ reported heart failure as the cause of death in 187 of 420 cases, or 44.5 per cent. If they included the coronary group, it was stated that 254 deaths, or 60.4 per cent, occurred from heart failure. In the present study we noted that 263, or 79.4 per cent, of 331 cases had cardiac hypertrophy.

In cases of renal arteriosclerosis Russell²⁰ found no evidence of renal impairment apart from the occasional excretion of a trace of albumin; all abnormalities in the tests for renal efficiency, complicated by heart failure, she believes, were such as known to be caused by heart failure. In our 23 cases of renal failure, heart failure as an important influence in the development of renal insufficiency was excluded. Patients with a combination of heart failure and renal failure were placed in the heart failure class. That a diminished renal function may occur ultimately in benign slowly progressive forms of renal arteriosclerosis is indicated by three cases reported by Van Slyke, and others²¹. The occurrence of renal failure in the course of hypertension with renal arteriosclerosis does not indicate that the case belongs to the malignant group any more than does the onset of cardiac failure or cerebral hemorrhage. As a consequence of hypertension and arteriosclerosis the lumina of the renal

arteries and arterioles often became so narrowed that an ischemic atrophy of the kidneys followed. In sharp contrast to the cases in group 3, the process in group 2 appears to develop slowly. Histologically no necrosis is seen, but a generalized arteriosclerosis of the larger and medium sized arteries is present with a focal arteriosclerosis of the smallest arteries and arterioles. The amount of fatty and hyaline degeneration and advanced arteriosclerosis is never so extensive as in group 3. Occasionally this benign process

gradually leads to almost complete fibrosis of a sufficient number of the glomeruli to produce renal failure. We observed 23 such cases, or 7.6 per cent, in group 2. Owing to the slowness of progress of the arteriosclerotic process in group 2, patients lived longer free from complications than those in group 3. Consequently there was a decided contrast in the age incidence of the two groups as shown in table 3. Most cases of essential hypertension never progress into group 3 (malignant type), but they end fatally from some

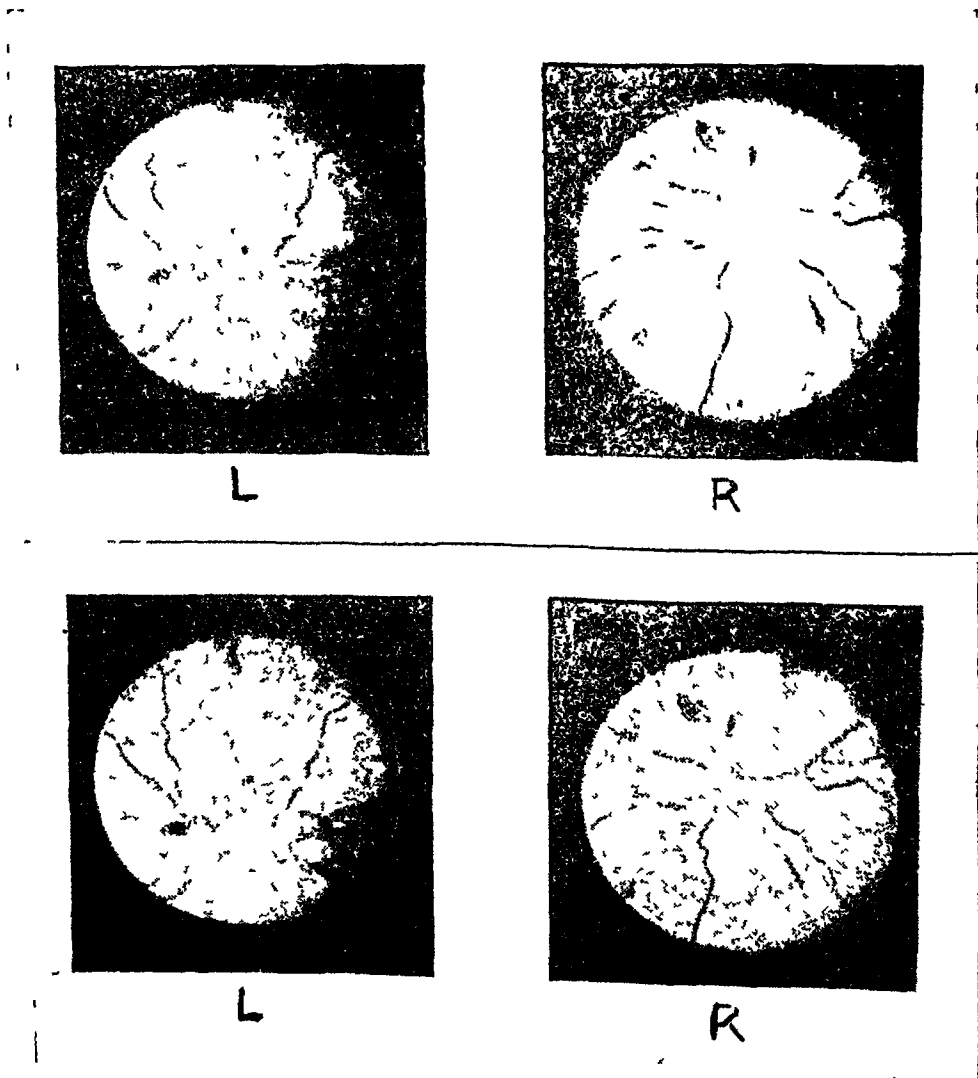


FIG 6 (Group 3). A photograph of the eye grounds. The choked disks, the tortuous thin arteries invisible in places, the distended veins, the fresh hemorrhages with areas of white patches present a typical picture as seen in Group 3

complication of simple arteriosclerosis in group 2. The reasons are not clear why a few patients with simple arteriosclerosis develop into the rapidly progressing type with necrotic lesions in arterioles. The explanation advanced by Volhard and Fahr² assumed that a toxic inflammatory factor was added to a kidney already damaged by arteriosclerosis. They first clearly differentiated between essential hypertension with and without renal failure and described the histological lesions found in the kidneys of each type. To the case of hypertension with simple renal arteriosclerosis with no renal insufficiency they applied the term "benign", and the term "combination form" or "malignant" was used to designate cases of hypertension which developed renal failure and uremia. They believed that the benign and malignant renal sclerosis were different forms of disease and not different stages. The considerable criticism that followed their publication dealt chiefly with their interpretation of the glomerular lesions of the malignant form. As stated by Fahr²² the clinical differentiation between benign and malignant forms was readily accepted, but a unanimity of opinion concerning the pathogenesis of the two forms was difficult to obtain. Volhard²³ stated that after the criticism of Lohlein²⁴ he concluded that an added inflammatory factor was unnecessary to explain the tissue changes in malignant form. He also concluded that the lesions are the result of vasoconstriction of the afferent glomerular arterioles with subsequent nutritional disturbances in vascular system.

Fahr²⁵ maintained his opinion that

the proliferative processes could not be produced by arteriosclerosis alone and that a toxic factor must be added. Among those who supported Fahr's theory were Von Mueller²⁶ and Meyer²⁷ and others. That the separation of the benign from malignant forms is justifiable from the clinical but not from the anatomical standpoint was held by Lohlein²⁸. He stated that one deals not with two forms but only different stages of one process. Aschoff²⁹ did not recognize a (combination) malignant form. However, he believed that a "complication" form may exist, that is, a glomerulo-nephritis may become engrafted on a pre-existing renal arteriosclerosis. Arteriolosclerosis of the kidney was a term adopted by Herxheimer³⁰ for the condition resembling malignant renal sclerosis of Fahr. He disagreed with the histological distinction between benign and malignant forms of renal arteriosclerosis, and maintained that they are terms applied to different stages of the same process and not to separate forms. Jores³¹ believed, too, that malignant and benign forms were different only in degree of arteriosclerotic involvement of smaller arteries. In the benign form he believed there was a focal arteriosclerosis of arterioles while in the malignant form there was a diffuse involvement of arterioles with disintegration of glomerular units.

In an intensive review of 420 cases of primary hypertension Bell and Clawson¹⁸ found 36 cases with renal insufficiency, 27 of the 36 cases had a slowly progressive form of renal failure ending in uremia. The remaining nine cases were characterized by uremia coming on rapidly. Histologi-

cally there was necrosis of afferent glomerular arterioles with infarcted glomeruli. In four of the nine cases, acute inflammatory changes were seen in a few glomeruli. For the nine cases they applied the term "chronic hypertension with acute uremia". The syndrome of malignant hypertension was clearly defined by Keith, Wagener, and Kernohan⁵. They described the typical retinal changes and rapid downward course in conjunction with functional failure, not of one organ, but of several organs simultaneously. In their work they emphasized the importance of finding hypertrophy of the media of the arterioles of the skeletal

muscles and of internal organs. They maintained that this hypertrophy indicates severe hypertension with diffuse vascular involvement and that the ultimate prognosis is bad.

Fishberg¹² did not see any essential difference between the benign and malignant forms. He used the term "malignant phase of essential hypertension" to describe those cases usually called malignant hypertension. The so-called malignant form, he stated, comes on gradually in the course of benign hypertension.

More recently Klemperer and Otani¹³ discussed this subject at length. In conclusion they stated that essential



FIG 7 (Group 3) Section from eye seen in figure 6. The arterioles of the retina show necrosis of the walls with almost complete obliteration of the lumina. Hematoxylin and eosin stain.

hypertension with renal failure may be associated either with a slowly progressing type of arteriosclerosis leading to renal failure or with a more rapidly developing vascular change in which severe renal atrophy is absent. This latter form is the "malignant" phase, and must be divided into two classes based on vascular lesions. In one there was necrosis of the arterioles with extreme cellular intimal thickening of larger interlobular and arcuate arteries and degenerative, proliferative, and slight exudative focal glomerular lesions. They believed that an ischemic mechanism is responsible for these changes, and they designated these cases as the accelerated atherosclerotic form. In the other form they observed necrotic lesions associated with perivascular inflammatory reaction, endarteritis and periarteritis. They recognized this latter form in two cases, in both cases a definite morbid process was present, recognized as toxic in origin. For such cases they used the term arteritic form of malignant nephrosclerosis. After carefully re-studying our material several times we failed to discover more than one case which would fulfil the requirement of the arteritic type. In this case there was a periarteriolar leucocytic infiltration with a proliferative endarteritis. We were unable to recognize an additional toxic factor either clinically or at autopsy. From the results of our observations we favor the view adopted by those who believe that no additional inflammatory influence is necessary for the development of the change seen in the so-called malignant stage. There are undoubted cases coming within the malignant class that represent the ef-

fects of a toxic arteriosclerotic combination. Such cases are described by Klemperer and Otani³³ and appear to be identical with Fahr's descriptions.

Attention must be directed to the fact that in group 3 (malignant), there are various degrees of arteriolar damage. Vascular lesions may range from the pre-necrotic stage characterized by advanced arteriolosclerosis with complete occlusion of the lumina of arterioles to an extensive arteriolonecrosis accompanied by peri-arteriolar and interstitial leucocytic reactions. Necrotic lesions of the arterioles may be sparsely scattered throughout the kidney being observed only after thorough search or by serial sections, or they may be so numerous that in every section many are seen. As shown in table 1 all patients that fulfill the requirements for a place in group 3 do not die of renal insufficiency. Those patients with the most fulminating form of renal failure dying of sudden onset of uremia had the most destructive forms of necrotic lesions in the kidney. Hypertrophy of the media of arterioles in skeletal muscles, and in internal organs has been emphasized by Kernohan, Anderson, and Keith³⁴ in cases of severe benign and malignant hypertension. They believed this hypertrophy of the media indicated a poor prognosis. Hypertrophy of the media in arterioles of skeletal muscles was present in some cases in group 2 as well as in all cases of group 3. With respect to hypertrophic changes in the media of renal arterioles there was more uncertainty. In some kidneys from both groups 1 and 2, moderate medial thickening was frequently seen. This thickening was found

not always to be hypertrophy of muscle tissue but due in places to degenerative changes in the media. We believe that medial hypertrophy may exist in arterioles of internal organs but it is not a constant feature of any group. On the other hand hypertrophy of the media in arterioles of skeletal muscle is a constant feature of group 3 and is associated with persistent and severe hypertension.

SUMMARY

1 Three hundred and seventy-five cases of essential hypertension are analyzed. On each of these postmortem examination was made.

2 The cases are divided for convenience of study into three stages: functional, arteriosclerotic, and arteriolonecrotic. The clinical signs and symptoms and the causes of death in each stage are considered.

3 Retinal changes were observed typical of the various stages.

4 Detailed postmortem pathological data, gross and microscopic, are

presented covering weight of hearts, size and structure of kidneys, arteriosclerosis, and necrosis of blood vessels of involved organs.

5 Unifying features of all stages are hypertension, cardiac hypertrophy, and arteriosclerosis. The chief complications are apoplexy, heart failure, and renal failure. Arteriosclerosis of the renal vessels is a constant and characteristic feature of essential hypertension at autopsy. Particular attention is given to the syndrome of so-called malignant hypertension.

6 Histologically the principal lesion is an arteriosclerosis. The wide variety of symptoms and signs appears to depend upon the extensiveness, the rate of progress, the severity, and the location of the arteriosclerosis.

7 The clinical and histological observations on group 3 (so-called malignant hypertension) differ from those in group 2 (benign) only in degree. All of the symptoms and histological lesions observed, we believe, may be produced by arteriosclerosis alone.

REFERENCES

- ¹VOLHARD, F. in *Handbuch d. inneren Medizin*, G. von Bergheim und R. Staehlin, 1931, Julius Springer, Berlin, vi, part 2, 1556.
- ²VOLHARD, F., and FAHR, T. *Die Bright'sche Nierenkrankheit, Pathologie und Atlas*, 1914, Julius Springer, Berlin.
- ³MURPHY, F. D., and GRILL, J. So-called malignant hypertension, a clinical and morphological study, *Arch. Int. Med.*, 1930, xli, 75-104.
- ⁴O'HARE, J. P., and WALKER, W. G. Arteriosclerosis, *Arch. Int. Med.*, 1924, xxxiii, 343-349.
- ⁵KEITH, N. M., WAGENER, H. P., and KIRKNOHAN, J. W. The syndrome of malignant hypertension, *Arch. Int. Med.*, 1928, xli, 141-188.
- ⁶FISHBERG, A. M., and OPPENHEIMER, B. S. The differentiation and significance of certain ophthalmoscopic pictures in hypertensive diseases, *Arch. Int. Med.*, 1930, xli, 901-920.
- ⁷WAGENER, H. P. Retinal vascular changes in hypertension, *ANN. INT. MED.*, 1930, iv, 222-226.
- ⁸MCGREGOR, L. Histological changes in the renal glomerulus in essential (primary) hypertension, study of fifty-one cases, *Am. Jr. Path.*, 1930, vi, 347-366.
- ⁹ALLBUTT, C. *Disease of the arteries including angina pectoris*, 1915, Macmillan and Company, London, 1, 381.
- ¹⁰MAHOMED, F. A. Chronic Bright's disease without albuminuria, *Guy's Hosp.*

- Rep, 1881, xxv, (Third Series), 295-416
- ¹¹MOSCHCOWITZ, E Hypertension, its significance, relation to arteriosclerosis and nephritis and etiology, *Am Jr Med Sci*, 1919, clviii, 668-684
- ¹²AYMAN, D, and PRATT, J H Nature of the symptoms associated with essential hypertension, *Arch Int Med*, 1931, xlvii, 675-687
- ¹³DAVIS, D The nature of the symptoms in essential hypertension, *Am Jr Med Sci*, 1931, clxxx, 850-857
- ¹⁴RISEMAN, J E F, and WEISS, S The symptomatology of arterial hypertension, *Am Jr Med Sci*, 1930, clxxx, 47-59
- ¹⁵ROLLESTON, H High blood pressure from the clinical aspect, *Lancet*, 1926, ii, 1203-1207
- ¹⁶FISHBERG, A M Hypertension and nephritis, 1930, Lea and Febiger, Phil, 410
- ¹⁷HERXHEIMER, G, and SCHULZ, K Statistisches zum Kapitel Bluthochdruck, Herzhypertrophie, Nierenarteriosklerose, Gehirnblutung nach anatomischen Befunden, *Klin Wchnschr*, 1931, x, 433-438
- ¹⁸BELL, E T, and CLAWSON, G J Primary (essential) hypertension, a study of four hundred and twenty cases, *Arch Path*, 1928, v 939-1002
- ¹⁹SHAPIRO, P F Malignant nephrosclerosis, pathogenesis, *Arch Int Med*, 1931, xlviii, 199-233
- ²⁰RUSSELL, D S A classification of Bright's disease, *Med Res Council*, 1929-30, Spec Rep Ser, No 142, His Majesty's Stationer's Office, 131
- ²¹VAN SLIKE, D D, and OTHERS Observations on courses of different types of Bright's disease and on resultant changes in renal anatomy, *Med*, 1930, ix, 257-386
- ²²FAHR, T Über die Beziehungen von Arteriosklerose, Hypertonie und Herzhypertrophie, *Virchows Arch f path Anat*, 1922, ccxxviii 41-63
- ²³VOLHARD, F in *Handbuch d inneren Medizin*, G V Bergheim und R Staehlin, 1931, Julius Springer, vi, part 2, 1561
- ²⁴LOHLEIN, M Über Schrumpfnieren, *Beitr z path Anat u z allg Path*, 1917, lxiii, 570-632
- ²⁵FAHR, T Quoted by Volhard (foot-note 22)
- ²⁶VON MUELLER, F Veröffentlichungen aus dem Gebiete des militäre Sanitätswesen 1917, A Hirschwald, Berlin, lxxv, 45
- ²⁷MEYER, O Über das Vorkommen und die Bedeutung entzündlicher Gefäßveränderungen in den Nieren mit besonderer Berücksichtigung der Glomerulitis, der sekundären und genuinen Schrumpfnieren, *Verhandl d deutsch path Gesellsch*, 1921-23, xiv, 352-363
- ²⁸LOHLEIN, M Zur Nephrocirrhosis Arteriosclerotica, *Med Klin*, 1918, xiv, 136-137
- ²⁹ASCHOFF, L Quoted by Volhard in *Handbuch d inneren Medizin*, G V Bergheim, und R Staehlin, 1931, Julius Springer, Berlin, vi, part 2, 1559
- ³⁰HERXHEIMER, G Über Arteriolonekrose der Nieren, *Virchows Arch f path Anat*, 1924, ccli, 709-717
- ³¹JORES, L Über den pathologischen Umbau von Organen (Metallaxie) und seine Bedeutung für die Auffassung chronischer Krankheiten insbesondere der chronischen Nierenleiden (Nephrocirrhosen) und der Arteriosklerose, nebst Bemerkungen über die Namensgebung in der Pathologie, *Virchows Arch f path Anat*, 1915, ccvii, 14-38
- ³²FISHBERG, A M Hypertension and nephritis, 1930, Lea and Febiger, Phil, 418
- ³³KLEMPERER, P, and OTANI, S "Malignant nephrosclerosis" (Fahr), *Arch Path*, 1931, vi, 60-117
- ³⁴KERNOHAN, J W, ANDERSON E W, and KIRBY, M The arterioles in cases of hypertension, *Arch Int Med*, 1929, xlix, 395-423

Hypertension*†

A Study of Two Hundred Two Cases Followed for an Average of Ten Years—With Remarks on Causes and Treatment.

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HYPERTENSION has been the subject of hundreds of articles and a considerable number of books during the last twenty years. Cardiovascular consultants and insurance companies have furnished most of that is written on end results.

Actuarial experience gives an extremely gloomy picture of the outlook for hypertension. Insurance records are based, however, on approximately 90 per cent males and exclude, for manifest reasons, all hypertension cases discovered at the time of examination. Cardiovascular consultants see chiefly cases who are sick with circulatory disturbances and hence see a more or less selected group of patients. We have been able to find no follow-up studies on unselected hypertension cases.

Two years ago we reported a series of cases obtained by reviewing 10,000 consecutive histories of general examinations made before 1925. We took for study all cases whose blood pressure was found definitely high,

using cases in which the systolic pressure was reported as 175 plus or the diastolic pressure 100 plus. Cases with readings below these figures were omitted because there is some question to whether temporary causes, particularly nervous, may occasionally give a reading up to these points. Thus we obtained a consecutive series of hypertension cases, unselected except by the fact that some complaint made them come in for a general examination.

Our clinic sees in each decade approximately an equal number of men and women, yet hypertension was found twice as frequently in women (64 per cent) as in men (36 per cent). In each decade between 30 and 70 years the percentage incidence of hypertension in women was approximately double that seen in men. Yet more than half of the women were without hypertensive symptoms, whereas hypertension in men was usually accompanied by symptoms. The large symptomless group of females with hypertension is not seen in cardiovascular clinics or by life insurance companies, and hence is not included in hypertensive follow-up studies.

*From the Mason Clinic, Seattle, Washington.

†Presented at the San Francisco Meeting of the American College of Physicians, April 6, 1932.

FOLLOW-UP STUDY

A follow-up study made two years ago gave information on the condition of 202 patients after an average of eight years. One-half (50 per cent) were dead. The female mortality was 42 per cent, whereas the male mortality was 79 per cent. About three-quarters of all deaths resulted from hypertensive disease, usually failure of heart or of cerebral circulation and occasionally nephritis. One-quarter of all deaths resulted from other causes.

We have followed 101 patients living two years ago down to the present. The gross mortality now is 60 per cent, but female mortality is 50 per cent and male mortality is 82 per cent, after an average of ten years. No male with marked hypertension still survives. Of 66 females surviving, 39 (59 per cent) are relatively symptom free, whereas of 13 surviving males 3 (24 per cent)

are relatively symptom free. Seven females are still alive in spite of marked or extreme hypertension discovered ten years ago.

Only two instances of recovery of a normal blood pressure have been noted.

These laborious follow-up studies and study of clinical histories have led to much reflection on the causes and treatment of hypertension.

CAUSES OF HYPERTENSION

Experimental hypertension has been produced by (1) various pressor substances, (2) removal of depressor nerves, (3) diffusely increasing intracranial pressure, and (4) experimental renal lesions which partially obstruct renal circulation. It should be noted that these experimental methods work through the sympathetic nervous system.

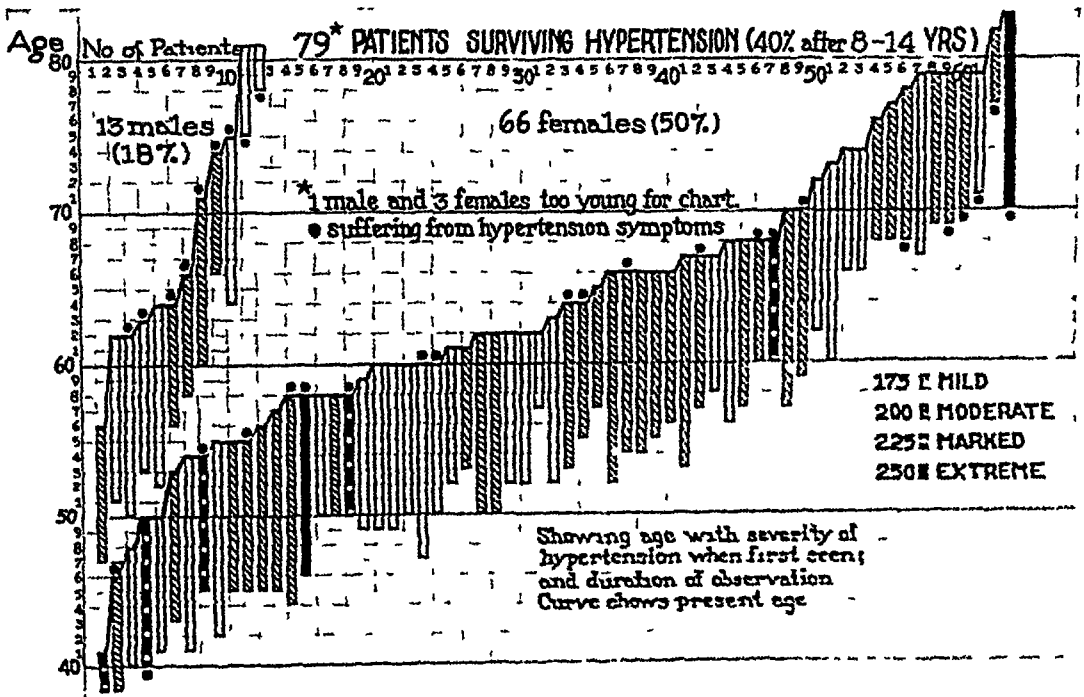


FIG 1

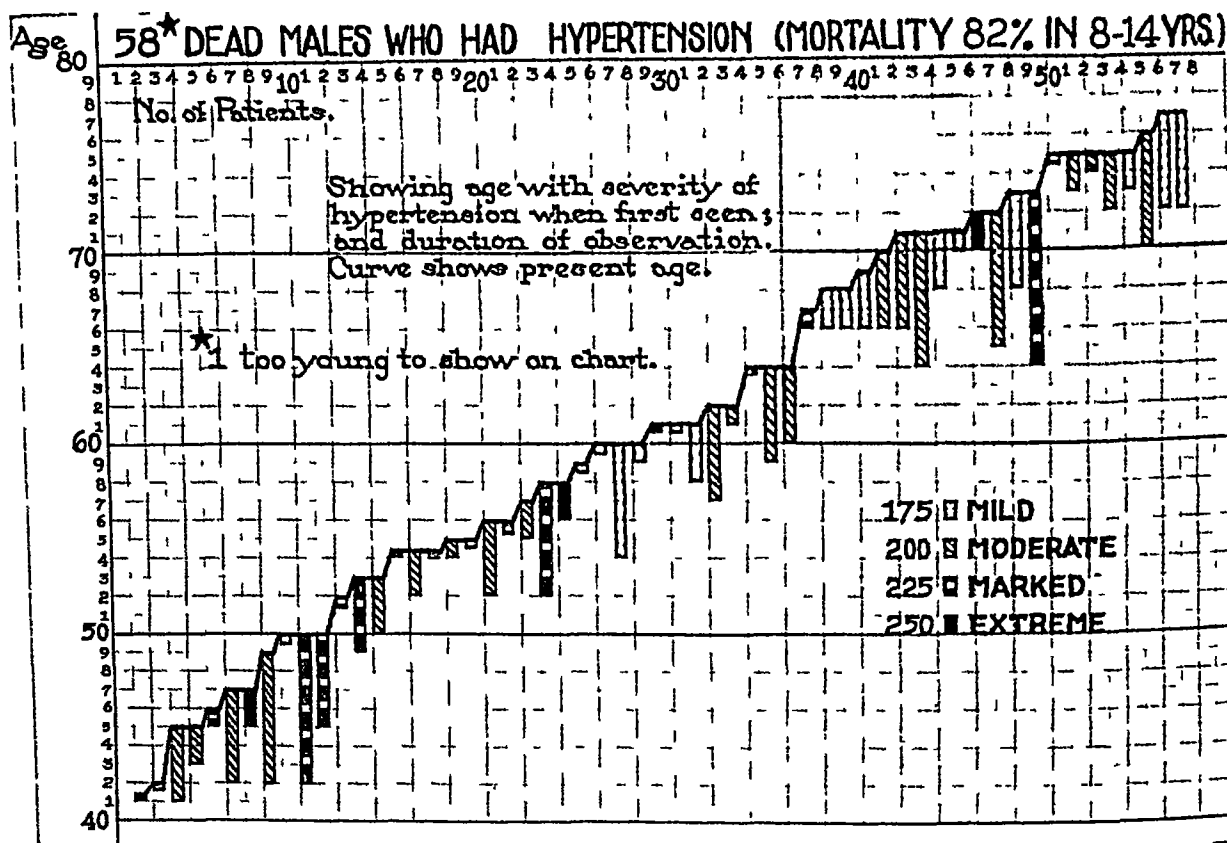


FIG 2

Clinical hypertension has been variously classified. The classification that seems to us reasonably complete is

- 1 Physiologic
- 2 Circulatory defects
- 3 Paroxysmal hypertension
- 4 Toxic
- 5 Renal
- 6 Neurogenous vasospasm

The last three groups include nearly all cases of clinical hypertension, and it is with these that we are here concerned.

Toxic hypertension includes cases due to known toxins which affect the kidneys, such as lead, mercury, and the toxins of the eclamptic state. Anaphylactic hypertension must be included here as well as the hypertension due to the toxic goiter. Hypertension due solely to toxic goiter is never high,

rarely as high as 175 mm, and is relieved by thyroidectomy. Higher readings than these in toxic goiter cases are not relieved by thyroidectomy, being due to essential hypertension associated with, but not due to, thyrotoxicosis.

Renal hypertension is found with chronic interstitial nephritis, chronic urinary obstruction, and often with polycystic kidney disease. It would seem that, as with experimental renal hypertension, chronic lesions offering obstruction to renal circulation are accompanied by hypertension of a compensatory nature. When such chronic obstruction can be relieved (as with prostatic cases) a normal blood pressure will be restored if there is not too much renal damage. Apparently there is a defensive compensatory angio-

spasm which automatically raises blood pressure as necessary to give an adequate renal circulation

Increasing intracranial pressure likewise automatically raises blood pressure sufficiently to maintain a cerebral circulation. Cushing's experiments have shown that when intracranial pressure is raised the blood pressure shows a corresponding rise

We see, then, that the cerebral and the renal circulations, necessary to life, are preserved by a rise in blood pressure to compensate for chronic partial circulatory obstruction in these organs, and the rise persists during the period of obstruction. Chronic partial obstruction of the cerebral circulation by increased intracranial pressure results in early deaths unless relieved. In the renal circulation such chronic obstruction may exist for months or years, with increasing blood pressure to

compensate for increasing renal damage

Essential hypertension brings us to a group of cases in which the blood pressure is high, without evident pathology to account for it. By far the greatest number of cases of hypertension fall into this group. It would seem that some constitutional tendency in the vegetative nervous system is responsible for the condition rather than unrecognized gross or microscopic lesions or retention of toxins. We recognize a hypotensive group of people, who may live long lives because lack of nervous endurance makes it impossible for them to wear out physically. We should recognize a hypertensive group, in whom the constitutional tendencies of the vegetative nervous system lead to generalized angiospasm with resulting hypertension. Early in this state of affairs there are no clinical symp-

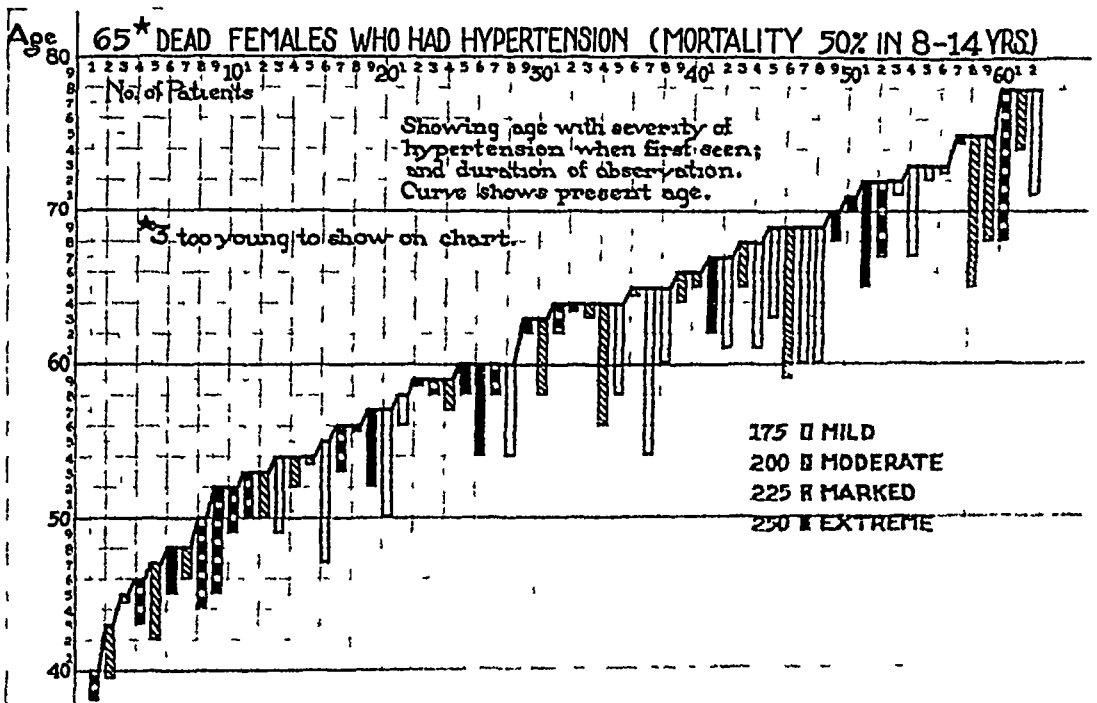


FIG 3

toms and the patient may appear quite normal. Later, depending on the resistance of the vital organs and the arteries to stress, we see progressive wear on heart and vessels. Results of such hypertonicity of the neuro-vascular control of spasm vary from the early and acute breakdown, with arteriolar necrosis, of malignant hypertension in youth to the chronic myocardial and vascular degeneration of increasing age. In certain instances the patient may even reach a ripe old age relatively free from symptoms in spite of an extreme hypertension.

It has been stated that hypertensive disease runs in families. We have found a family history suggestive of hypertensive disease in more than one-third of all cases of hypertension, but approximately the same percentage of hypertension in family histories is found in all family histories of patients, regardless of complaints. In spite of these facts, most physicians feel that there is a strong family tendency toward hypertension in certain instances.

Available clinical and laboratory evidence suggests that hypertension must be regarded as the result of a generalized angiospastic state, a constitutional vascular hypertonus inherent in the individual. It rarely becomes evident before 40 years of age. It is far more serious in younger people. It is less serious but more frequently found in women than in men.

TREATMENT

Treatment based upon this conception becomes a matter of relief of stress, particularly mental stress, and of moderation of habits. Medical

treatment is reserved for relief of complications, and these may not develop for many years. Cardiac failure is the usual symptom that requires relief, with cerebral vascular symptoms next most common. Sedatives, both mental and physical, are required, with all the reassurances and encouragement that can be given. Bromides, barbitol derivatives, etc. are of great help.

Venesection is frequently indicated for relief of symptoms, particularly headache. The blood pressure is reduced only transiently by this procedure, yet subjective relief may last over weeks or months. Nitrites are occasionally valuable in relieving hypertensive headaches.

Weight reduction is always advisable in the obese. We usually prescribe a well balanced diet, low in salt and in proteid foods. Every effort should be made to avoid any dietary insufficiency leading to unnecessary anemia and loss of strength; and this can easily happen if the conscientious patient is advised to eat no meat or eggs.

Attempts at specific medication are always interesting. Aylen of Boston has found no drug of greater value than could be accounted for on a psychotherapeutic basis. To enumerate drugs recommended would make a long list. We may mention watermelon seed, mistletoe, liver extract, potassium sulphocyanate, and bismuth subnitrate as recent suggestions that have not stood the test of therapeutic practice. Possibly some day some specific remedy may be discovered. It seems to us doubtful if we can change constitutional tendencies inherent in the patient, even though we may greatly

relieve symptoms which result from the continuation of these tendencies

Fear, anxiety, and introspection are the most troublesome symptoms associated with hypertension. Unfortunately they are sometimes implanted and fostered by the physician. Fear of the consequences of hypertension causes more suffering for many patients than do all the later severe complications which may occur.

SUMMARY

In conclusion, we find that

1 Hypertension is twice as frequently found in women

2 The mortality rate after ten years is twice greater in men

3 Hypertension results from a constitutional hypertonicity of the autonomic neurovascular control in the large majority of instances and is a compensatory angiospasm in the others

4 Treatment of uncomplicated hypertension is a matter of mental and physical hygiene rather than of drugs

5 Treatment of late results of hypertension requires skillful use of medical and physical measures, added to psychotherapeutic measures

6 The physician who is a good and cheerful psychologist will be the most successful in relieving the symptoms of hypertensive cardiovascular disease

Thallium Poisoning

A Report of Three Cases*

By JAMES LEHMAN, M D , and LEO GARFNEY, M D , *Cleveland, Ohio*

THE increasing incidence of thallium poisoning, following the use of depilatory creams has prompted us to report the following cases which have been under observation recently at the Cleveland Clinic. In all three cases the history included a similar statement, namely, that the patient had used "Koremlu", a depilatory cream.

Several cases of thallium poisoning have been reported. Lansbury¹ of the Mayo Clinic reported the first case. A short time later, Duncan and Crosby² of the Cleveland Clinic reported a similar case. Greenbaum and Shamberg³ have also reported cases. The Bureau of Investigation of the American Medical Association has published a report¹ on the chemical analysis of "Koremlu", and branded it a dangerous depilatory, containing seven per cent of thallium acetate. Sabouraud, after an extensive experience with the use of thallium as a depilatory is said to have given up its use. (See Paris Letter, Jr Am Med Assoc, Jan 18, 1930.) Moreover, Sabouraud's original preparation called for an ointment with not more than one per cent of thallium acetate and the use of the oint-

ment in quantities not larger than the size of two kernels of wheat, to be applied not more than twice a day. In the directions for the use of "Koremlu", no mention is made of the amount to be used, nor the frequency of its application.

CASE I

A woman, 39 years of age, came to the Clinic on March 26, 1931, complaining of pain in both legs. She had been well until two weeks previous to her visit to the Clinic, when she noticed numbness and tingling in her toes. This progressed gradually until the entire lower extremities were involved. Two days before her admission to the Clinic the numbness was replaced by pain which was most severe in the knees and ankles, and it was necessary for the patient to remain in bed. The pain was confined to the lower extremities and was relieved somewhat by the application of heat.

The family and personal history had no bearing upon the existing condition.

The significant findings in the physical examination were the following: the hair was well nourished and was distributed normally, except for hypertrichosis of the face. The tonsils, which were of moderate size, were imbedded and contained débris and liquid pus. A complete x-ray examination of the teeth showed one carious tooth, periapical infection about the first and second premolars of the upper left, first and second premolars of the upper right, first molar of the lower left and second molar of the lower right jaw. The patient was advised to have these teeth extracted. The tongue was heavily coated, and a slight

*From the Cleveland Clinic, Cleveland, Ohio. Submitted for publication, November 12, 1931.

tremor was present. A special neurological examination by Dr W James Gardner gave the following positive findings: pain, deep tenderness and muscular weakness of both lower extremities, moderate hyperesthesia of the skin with no definite level, diminished plantar, patellar, Achilles and triceps reflexes.

The patient was admitted to the Cleveland Clinic Hospital with a diagnosis of toxic neuritis, carious teeth, and chronic tonsillitis. Further questioning of the patient brought out the fact that she had been using a depilatory cream, "Koremlu", applying it twice a day. We felt justified, therefore, in making a diagnosis of peripheral neuritis, due to the toxic effects of thallium absorbed from the depilatory cream.

TREATMENT

During her stay in the hospital, the patient was put at absolute bed rest and external heat was applied to the lower extremities. Passive motion and massage were instituted. She was also given an alkaline diuretic. The six diseased teeth and the tonsils were removed. On April 8, 1931, the patient was discharged somewhat improved.

On April 29 she reported that all pains had disappeared with the exception of some discomfort in the legs when fatigued. There was still a sensation of numbness in all the toes. Fatigue was marked, but there was good power in the dorsi-flexors.

The latest report from the patient was on July 22 when she stated that she was free from pain except for a slight prickling



FIG 1 Marked alopecia after using "Koremlu Cream" for removal of hair from the face

sensation or partial numbness after walking rapidly or great distances. For a month past she had noticed that her hair had been falling out.

CASE II

A woman, 28 years of age, was admitted to the Cleveland Clinic Hospital on April 21, 1931, complaining of aching pain in the thighs and legs, impairment of sensation in legs, arms, feet and hands, abdominal cramps not associated with nausea or vomiting, generalized weakness, inability to walk, loss of cranial, axillary and pubic hair, speech impairment, menstrual irregularity, restlessness, irritability and insomnia.

The patient was well until three and one-half months previous to her admission to the hospital. The symptoms were noticed from two to three weeks after she had started using "Koremlu" cream for the removal of hair from the face. This cream was purchased from a department store in Akron, Ohio, at a cost of \$10.00 for a small jar. The patient had been applying the cream once a day until she came to the hospital.

The first symptom noticed was the aching pain in the legs, especially in the calf muscles. After about a month she noticed that she was losing the power of her legs which became complete three weeks previous to her admission to the Clinic. Following this, abdominal cramps developed, which gradually increased in severity. There was no nausea, vomiting or diarrhea on taking of food. About six weeks after she started using the cream, her cranial, pubic and axillary hair began to fall out until almost complete alopecia resulted. The hair on the face was not affected. Generalized weakness gradually developed including impairment of sensation in the legs, arms, hands, and feet, the menstrual flow became very scant, the patient became restless and could not sleep. She had lost about five pounds.

The significant findings in the physical examination were as follows. The skin was rather dry and smooth, there was very little hair on the arms or legs and the loss of cranial hair was marked, the scalp was dry and scaly, the hair was dry and easily

pulled out. The eyebrows showed loss and what remained were easily pulled out. The tongue was coated and rather dry. The tonsils which were of moderate size contained debris and some infectious material. The abdomen was slightly tender just below and to the left of the umbilicus but no masses were found and there was no rigidity.

Marked tenderness was present over the posterior aspect of the thighs, and over the anterior and lateral portions of the legs, there was suggestive impairment of sensation over the inner aspect of the right leg, the muscles, especially of the thighs and legs, were flabby. The patellar and biceps reflexes were fairly active and equal, there was some numbness and tingling in the legs, feet and hands. Loss of motor power in the legs and arms was noted and the patient could stand for a few minutes only.

Dental examination revealed no devitalized teeth and no evidence of periapical infection; there were two extensive restorations, and the patient was advised to have these teeth tested for vitality, and to have them extracted if necessary.

Neurological examination revealed impaired gait, toe drop, bilateral partial paralysis of the lower extremities, bilateral atrophy and hypotonicity of the lower extremities, paresthesias of the legs and hands and impairment of sensation of the legs. The patient's voice was husky and she was mentally depressed.

About a week before her admission to the hospital the patient refused to have an exploratory laparotomy in order to determine the cause of the abdominal cramps.

Treatment

The patient was given 3500 c.c. of fluid over a twenty-four hour period. Sedatives were administered as indicated for pain or insomnia. A cradle was placed over the lower extremities to protect them from the weight of the bed clothes, and the soles of the feet were supported to overcome the footdrop. Calcium chloride was administered intravenously in doses of 20 c.c. of a five per cent solution every second day. After five injections, the symptoms became worse and this treatment was discontinued.

Heat, light and massage were applied to the lower extremities

When the patient was discharged after twenty days, her condition was slightly improved. The hair was still falling out but the pain in the extremities was less severe and the abdominal cramps were not so constant. The patient was less restless and slept better. She was still unable to walk, however, and the leg muscles showed increasing wasting. Bilateral toe drop and positive Babinski were still present and the reflexes were still diminished. Numbness and tingling were still present in the hands and feet. The general condition of the patient was somewhat improved, however, and she was less depressed.

A report from the patient's physician on July 7 stated that she had shown slight improvement since her return home but was still confined to her bed and unable to walk. Pain was still present in the legs but the abdominal cramps had disappeared. The leg muscles showed a moderate degree of wasting. The cranial hair had begun to grow and was about one and one-half inches long. The patient was receiving massage

and passive motion of the legs daily. She still required sedatives occasionally.

CASE III

A woman, 27 years of age, came to the Clinic on July 8, 1931, complaining of pains in the legs. The pain began about August 30, 1930, three weeks after she began using "Koremlu Cream" for the removal of hair from the face. In spite of the fact that the pain became worse as the patient continued to use the depilatory, she did not and had not to date connected the use of the cream with the pains, which she described as being dull and aching and made worse by motion. After two months the pain became so severe and constant that she was confined to bed. Her family doctor could not find the cause of the trouble and his treatment gave no relief. He finally sent her to a hospital in Pittsburgh, where a thorough study was made of the case. Just before going to the hospital, she began having cramplike pain in the abdomen. A gastro-intestinal series was done but no pathological condition was demonstrated. While in the hospital she stopped using the

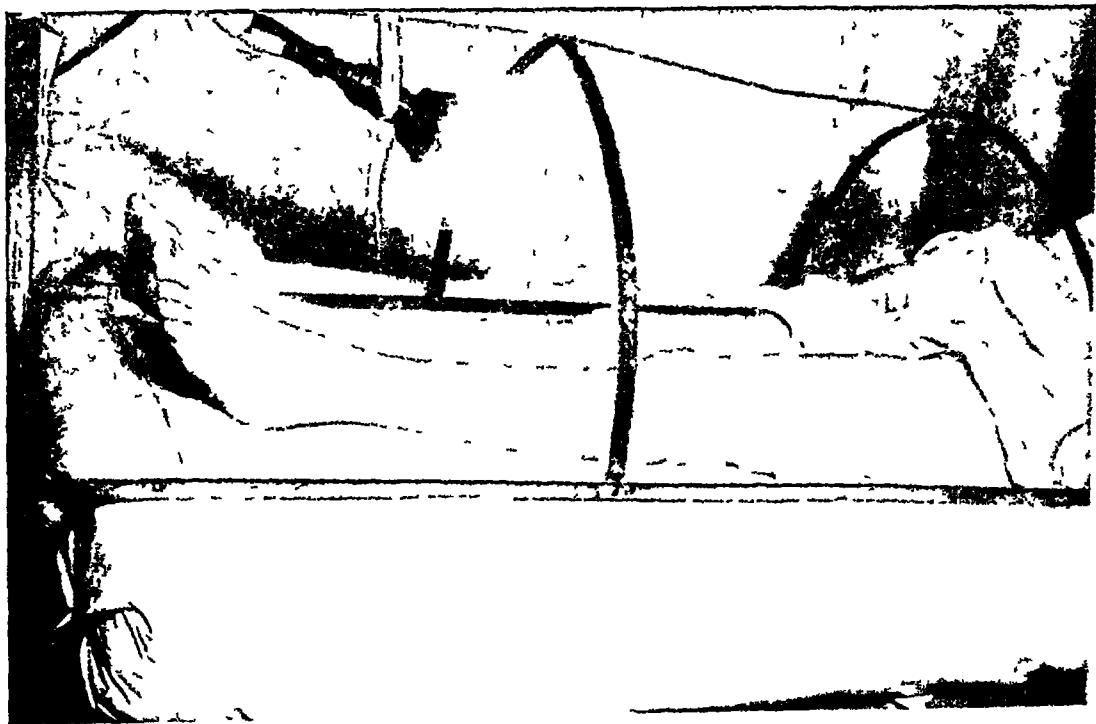


FIG 2 Foot drop and muscular atrophy of lower extremities in thallium poisoning

cream and at the end of three weeks she felt somewhat improved and was discharged. After she returned home she began using the cream again and the pain in the legs and abdomen returned. Associated with the pains at this time was a marked sensitiveness of the feet, which prevented walking.

After trying various treatments for two months she decided to go to Hot Springs, Arkansas, to take the baths. A few days after arriving there she finished her second jar of "Koremlu Cream" and was unable to buy any at Hot Springs. She took a series of baths and her health began to improve. She remained at the Springs for about four weeks. At the end of that time, nearly all the pain was gone and she was able to walk without any discomfort. The patient returned home and enjoyed freedom from pain for two months, during which time she was not using the cream. A short time later she bought another jar and began using it each night, and continued to use it up to the time of her admission to the Clinic. About three weeks later, the pain in the

legs, and sensitiveness in the feet and the cramps in the abdomen returned. The patient mentioned to several doctors that she was using "Koremlu Cream" but they all assured her that this could not be the cause of her trouble. She had had no loss of cranal, axillary or pubic hair.

Examination at the Clinic showed a well nourished woman, not actually ill. The only positive physical findings were atrophy of the left calf and thigh, to the extent of about one and one-half inches, and tenderness along the course of the nerves of the legs. No attempt was made to isolate thallium from the urine.

In view of the fact that the pain first occurred shortly after the patient started using the "Koremlu Cream" and because the pain disappeared when on two occasions she discontinued the use of the depilatory, we felt that we were justified in making a diagnosis of chronic thallium poisoning. The patient was advised to discontinue the use of the cream and to have light massage and light treatment for the legs.

REFERENCES

¹LANSBURY, J. A case of thallium poisoning. *Pro of the Staff Meet of the Mayo Clinic*, 1930, v, 323-325.

²DUNCAN, W. S., and CROSBY, E. S. A case of thallium poisoning following the prolonged use of a depilatory cream, *Jr Am Med Assoc*, 1931, xcvi, 1866-1868.

³GREENBAUM, S. S. and SHAMBERG, E. Reports of thallium acetate poisoning following the use of Koremlu. *Jr Am Med Assoc*, 1931, xcvi, 1868.

⁴A dangerous depilatory containing thallium acetate, *Jr Am Med Assoc*, 1931, xcvi, 629-630.

Newer Aspects in Parodontosis (Pyorrhea)*

By HERMANN BECKS, M D , D D S , *San Francisco, California*

OUR conceptions of the true anatomic conditions in the region of the tooth supporting tissues or "paradentium" (Weski) have recently undergone a definite change through the work of contemporary histologists and clinicians (Boenheim, Citron, Gottlieb, Haupl, Lang, Loos Weinmann, Weski)

This change in our ideas brought about a renewed interest in the etiologic and pathogenetic questions in parodontosis in all countries. Today after twelve years have elapsed there are still questions of fundamental importance which are under debate, the solution of which may not be reached in any short space of time. These are mainly histologic details which, however, are of immense importance to the practicing dentist; these he must know in order to be able to understand the etiology, pathogenesis, and therapy of the disease. Before these new conceptions can be adopted it will be necessary to throw overboard many antiquated theories, otherwise we will become involved in a maze of complicated ideas, from which it will be very difficult to extricate ourselves.

One of the greatest advances in the last few years in this particular field

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has been in the new terminology which was decided upon by vote of the Eighth International Dental Congress, at Paris, in August, 1931. I refer to the term "parodontosis", which replaces the old term "pyorrhea".

A classification has been adopted which includes all known types of the disease formerly called "alveolar pyorrhea", "periodontoclasia", etc. It groups all cases according to their clinical symptoms. The designations, as such, have been chosen to point to the pathogenesis of the disease.

CLASSIFICATION

- 1 Marginal suppurative gingivitis
Local manifestations
Superficial inflammation with discharge of pus at the gingival margin
Calculus
No distinct pocket formation
- 2 Parodontosis
 - a. Profound simple parodontitis
Local manifestations
Deep pocket
Pus
No loosening of the teeth
 - b. Diffuse dystrophy
Local manifestations
Irregular atrophy
Migration or loosening of teeth
No pus

c Complicated dystrophic paradentitis

Local manifestations.

Deep pocket

Pus

Eventual loosening of teeth or migration or both

The final phase of a, b, and c, is:

Loosening of teeth, deep pockets, pus

3 Alveolar atrophy

a Pre-senile atrophy (atrophia praecox)

Local manifestations

Early recession of the gingival margin

Horizontal atrophy of bone

b Senile atrophy

Local manifestations

The same as under "a", but at an advanced age

It is of especial importance to observe that in this classification the marginal suppurative gingivitis, which was formerly designated as "pyorrhea", has been separated from the large group of paradentosis. This has been done because such a marginal suppurative gingivitis with a slight discharge of pus exists over a period of years without developing into a paradentosis; i.e., without involving the deeper parts of the paradenium. Of course this condition may suddenly become an ulcerative type of gingivitis or paradentitis, which in the course of time involves the bone and leads to the clinical picture of paradentosis.

On the other hand the alveolar atrophy has also been separated from paradentosis because it represents a special group of diseases.

Paradentosis itself is subdivided into three main groups, which include all

types of this disease of the paradenium known at the present time. However, it may be emphasized that this classification is only tentative and has been adopted in order that practitioners of medicine and dentistry, as well as research workers, may be provided with a uniform working basis. Doubtless, it would be easier for the practitioner if a classification could be made which includes the etiological factors, i.e., if we could speak of a diabetic paradentosis, of a scorbutic or an arthritic paradentosis. However, our research has not progressed that far as yet.

There is a very definite conception of the disease connected with this new designation, which means more than just "pyorrhea", which is defined as "pus discharge from the gum pocket". We must try more than ever to forget the symptom of pus in establishing the diagnosis, since this does not indicate the condition of the tissues. Our observations should be directed toward the morphological and clinical changes to be treated and here we must be interested first in the factors which have led to these changes in the paradenium.

The paradentosis problem is a part of a constitutional problem. The *individual disposition* forms the nucleus of the susceptibility to paradentosis, which on the one side occurs as a result of systemic disease and on the other on the same basis as the disease itself. We speak of endogenous factors in collusion with well known exogenous factors, by means of which the paradentosis has gained a foothold. At the present time we have very little scientific information about these en-

ogenous factors, which influence the occurrence of paradentosis

In the etiology we differentiate today between two fundamental forms of paradentosis. First, that which is characterized by an inflammatory disappearance of marginal tissue, and second, one with a generalized tissue destruction. Although we have gained a vast amount of knowledge concerning the first type in etiologic and histopathogenic respects, there still exists a great hiatus in our knowledge of the etiology of the genuine type, which seems to be based on an abnormal condition in bone apposition and resorption, i.e., a lack of stability in bone metabolism (Loos, Weski). Several times Loos has expressed the opinion that this form of paradentosis, which is based on the instability of the bone metabolism, occurs as a result of an osteopathy with an endocrine genesis. We have not advanced beyond this point as yet and only recently in our laboratory at Hooper Foundation we were able to furnish for the first time the scientific proof of this theory by means of diet experiments in animals.

We will omit from the following discussion the marginal suppurative gingivitis, which is caused essentially by exogenous or local factors and concern ourselves only with that form of paradentosis which cannot be explained by local irritation only and must, therefore, fall in the field of investigation of the general system. We do not know definitely whether or not a special constitution of the capillary system of the parodontium or of the osseous system (Loos) brings about a susceptibility to the disease. However, we may accept this as an hypoth-

esis. At the present time, in all countries, workers are feverishly active in the endeavor to establish a relation between paradentosis and diseases of metabolism, diseases of the blood-forming organs, hormonal disturbances, and disturbances of the vegetative nervous system. Even though they have not become pathognomonic for paradentosis as yet, all investigations and examinations in this direction are extremely important for paradentosis as a medical problem.

If we start with the supposition, as already mentioned, that the osseous part of the parodontium primarily gives a constitutional basis for paradentosis or that through other endogenous factors the alveolar process undergoes changes which lead to the typical atrophic and dystrophic symptoms, an especially interesting field of investigation is that of calcium metabolism.

In the year 1929, I reported that the electrolytic content of the saliva in patients suffering from the so-called diffuse atrophy deviated from the normal. This was of importance because no studies in mineral metabolism had as yet been made. At that time I reported that in the saliva of seventeen cases of diffuse atrophy of the alveolar process the potassium and sodium contents were increased and the calcium and phosphorus contents were decreased as much as 25 per cent. At the same time a publication of Citron appeared covering the examination of serum calcium in patients with paradentosis and a few others along this same line followed (Kauschansky, Herz, Weinmann, Becks). Citron examined eighty-seven cases of para-

dentosis, which had not been classified exactly, for serum calcium and potassium. He also examined the basal metabolism, the specific dynamic action of foods, and microscopically the capillaries of the gum tissue. In these patients all laboratory findings showed some metabolic disturbance. Citron related these disturbances to a primary dysfunction of the glands of internal secretion. He classified them as thyroid, parathyroid, ovarian, and pituitary types of paradentosis and believed that they were a symptom of a general systemic disease. In these eighty-seven cases he found that the serum calcium value was between 8 and 9 mg. per cent in three cases, between 10 and 12 mg. per cent in seventy-three cases, and between 13 and 17 mg. per cent in eleven cases. This means that in the majority of cases suffering from paradentosis, the serum calcium content was increased.

Weinmann, one of the most enthusiastic supporters of the so-called diffuse atrophy as an independent disease, which is designated in the new classification as diffuse dystrophic type of paradentosis, found approximately the same percentages, while Herz found normal calcium values in most of his cases. Kauschansky found calcium values above 11 mg. per cent in 35 per cent of his cases (he examined 135 patients with "alveolar pyorrhea").

The weakest point in these publications is that the cases of "alveolar pyorrhea" were not classified. Frequently in scientific publications we find the same confusion that is prevalent among practitioners, i.e., a lack of the exact details of diagnosis. Weinmann is the only one who made

examinations exclusively of cases with diffuse dystrophic paradentosis, while a mixed material was used by other investigators, which may be composed to a large extent of cases of simple gingivitis, designated today as marginal suppurative gingivitis, and naturally in these cases we cannot expect to find any change in calcium metabolism. The conclusions which were drawn from these findings are, therefore, without value.

The cases of paradentosis which I have examined within the last year have been grouped according to the new classification. Only cases of the diffuse dystrophic type were examined; i.e., cases of Gottlieb's diffuse atrophy. These were cases which roentgenologically showed extreme resorption of the alveolar process. The patients were young adults between the ages of twenty and thirty-five years. The resorption was too far advanced to be accounted for by the age of the patient and the degree of inflammation present. There existed a tendency to migration and slight loosening with pocket formation.

The majority of cases—there were only a very few exceptions—showed *an increase of the amount of serum calcium*, i.e., we confirmed the statements of Citron, Weinmann, and Kauschansky. The serum calcium values reached as high as 18.15 mg. per cent. The cause of this increase in the amount of serum calcium is still problematic. Citron believes that the hypercalcemia must be traced to an increased function of the parathyroids. He bases his conception on the fact that an elimination of the parathyroid function leads to an increase of

potassium and to a decrease of the calcium in the blood while the reverse condition would mean an *over-function* of the gland. Experimentally this has been proven by the administration of large doses of Collip's parathormone.

The potassium-calcium quotient of normal cases gives a practical index which can be used in determining an unbalanced condition. If the normal potassium content is about 20 mg per cent and the normal calcium value lies between 9 and 11 mg per cent, the potassium-calcium quotient is about 1.6 to 2.0.

In the thirty-seven examinations of Weinmann, in which he found hypercalcemia twenty-seven times, the potassium-calcium quotient was below normal only eight times, while it was above seven times. This vacillation of the quotient, of course, does not allow any conclusions concerning the participation of the parathyroids in this process. Weinmann even expresses doubt that the increase in serum calcium may be traced back to a mobilization of calcium salts from the bone.

In our examinations, we found that the serum potassium value was just as frequently increased as decreased. *However, the striking fact was established that in the twenty-four cases examined, eleven cases showed a low, four a high, and nine a normal potassium-calcium quotient.* This seems to show that the increase in blood serum calcium parallels a relatively low potassium value, which led in the majority of cases to the low potassium-calcium quotient. On the other hand a relation to an endocrine disturbance seemed to exist in our cases, which is in contrast to the findings of Weinmann.

The porotic jaws which we observe so very frequently in roentgenograms suggest that a disturbance in the balance of bone apposition and resorption may be present. Whether this disturbance is produced by the endocrine system, by a deficient diet, or constitutional anomalies is rather a secondary question. First, it must be proven scientifically that such a disturbance really exists and for this purpose the calcium analyses of the blood serum alone are of no value whatsoever. As already shown, they can be used in connection with potassium analyses and may help explain the participation of the endocrine system. However, in order to be able to draw conclusions concerning the participation of the osseous system we must consider other factors. Of these I might mention the phosphorus metabolism in its relation to calcium metabolism, further, the carbon dioxide capacity of blood, the basal metabolism, and the specific dynamic action of proteins.

From the investigations of Dr. E. V. McCollum and his co-workers, we know that the growth of the osseous system depends on the vitamin D content of the food and the correct calcium-phosphorus ratio. If this is undisturbed, i.e., no relative excess of one or the other, a comparatively small amount of vitamin D is sufficient to guarantee good calcification of the osseous system. However, if there is an excess of one or the other, small quantities of vitamin D do not suffice to prevent severe disturbances of calcification. In other words if the calcium-phosphorus ratio is disturbed an abundance of vitamin D must be given in order to compensate for the im-

balanced ratio. Otherwise the typical picture of rickets results.

If we consider in this connection the osseous system of an adult for some time on an unbalanced diet, which for instance did not contain calcium enough in proportion to phosphorus, osteoporotic changes develop which manifest themselves in the jaws by a destruction of the trabeculae and an enlargement of the marrow spaces. The same osteoporotic changes of the alveolar process are found if a growing dog is fed with a basal diet and a normal salt mixture, but without the addition of cod liver oil (vitamin D). Roentgenograms show the jaws of such animals to be less dense than those of animals receiving sufficient vitamin D.

If we omit a large part of the calcium in the diet, as well as vitamin D, the typical picture of diffuse *dystrophic* paradentosis develops instead of an osteoporosis. We find typical horizontal and vertical types of atrophy, as well as periodontal dystrophy. These lead clinically to a loosening of the teeth with a tendency to migration, which is especially marked in the region of the anteriors.

The calcium metabolism, therefore, bears a very close relation to the vitamin D content of the food. On the other hand, we know that the calcium metabolism is regulated and controlled by the endocrine system, especially by the parathyroids. According to our experiments, vitamin D represents in a certain way a mediator between the calcium metabolism and the endocrine system. If the osseous system in these cases of paradentosis is primarily involved to a certain extent—which we must believe from our experiments—

the question arises in what way the calcium-phosphorus metabolism is changed.

In our blood serum analyses of patients suffering from diffuse dystrophic paradentosis we found an *increased amount of calcium*, as already mentioned. The inorganic phosphorus content is decreased in 50 per cent of the cases and in others it is normal. The calcium-phosphorus quotient, which lies for normal serum between 2.4 and 3.0, is increased in about 50 per cent (of the 25 cases examined).

The examination of the saliva revealed in about 90 per cent of these cases a *decreased calcium amount* with normal or slightly increased phosphorus values. This results in a low calcium-phosphorus quotient, this is exactly the reverse of what we found in the blood. We see, therefore, that we are dealing with a definite disturbance in the potassium-calcium and the calcium-phosphorus quotient in these cases of paradentosis.

Clinically we observe that bone substance is being lost and biochemically we find a hypercalcemia with a frequent relative or absolute lack of phosphorus in the blood serum.

In the mixed resting saliva, however, we find a hypocalcemia and a normal or relatively high phosphorus content.

These findings have carried us one step further in the recognition of these types of paradentosis. They may be interpreted to mean that either an endocrine disturbance, perhaps pluri-glandular disturbances, a deficient diet, infectious disease, or other metabolic diseases mobilize calcium salts from the bone and perhaps from the teeth,

which leads to an increase in the amount of calcium in blood serum. This increase of serum calcium in most of the cases is not accompanied by an increase of the blood phosphorus resulting in a relatively high calcium-phosphorus quotient and a low potassium-calcium quotient. Since we find in the mixed saliva of these patients a low calcium content with a relatively high phosphorus content, which is exactly the opposite of what we find in the blood, we must trace this to the factors influencing the secretion or excretion processes in hypercalcemia.

This shifting in the calcium-phosphorus quotient encourages me to define more precisely that type of paradentosis with which the medical

and dental professions are so often confronted. *The diffuse dystrophic paradentosis* is characterized clinically by a primary bone disturbance on the basis of an osteopathy with a tendency of the teeth to migration and loosening without inflammatory symptoms. This osteopathy is so slight that no clinical manifestations of disturbance of the general osseous system are to be found. The biochemical aspect is characterized by a high calcium-phosphorus ratio of the blood serum. The total serum calcium amount is increased with a relative or absolute lack of inorganic phosphorus. The potassium-calcium ratio of blood serum is frequently found below normal.

The Report of a Case of Early Hodgkin's Disease Secondarily Infected with a Strain of Pathogenic Monilia *

By SAMUEL R. HAYTHORN, M D, F A C P., GEORGE H. ROBINSON, Ph D, and
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THE patient concerned in this report was a man 70 years of age who presented an unusual combination of clinical and pathological findings. The diagnosis of Hodgkin's disease was based entirely on the microscopic changes and was not suspected during life or from the gross findings at autopsy. The outstanding features of the case were inflammatory lesions of the lungs and spleen and the isolation of a pathogenic strain of monilia. The unusual lung lesions were found microscopically to be nodules of organizing pneumonia through which numerous large cells of the "Dorothy Reed" type were distributed, and which we interpreted as having been attracted to the site by the irritating influences of the monilia. There were several other unusual circumstances not commonly associated with Hodgkin's disease such as the age of the patient, the atypical blood picture, the absence of enlarged glands and the unusually high fluctuations of the temperature.

*From the William H. Singer Memorial Research Laboratory and the Allegheny General Hospital, Pittsburgh, Pa. Received for publication, September 18, 1931.

CASE REPORT

Abstract of Clinical History *First Admission*

Mr. W. A. N., aged 70 years, a farmer, was admitted to the service of Dr. Lloyd W. Johnson on August 15, 1928. There was no family history of neoplasms and the patient's habits were of the best. He was an active farmer, working from twelve to fourteen hours daily until one week before his first admission and then complained chiefly of chronic arthritis.

He was admitted for chills, fever and arthritis. No satisfactory diagnosis was made and he was discharged in two weeks, much improved. All examinations were negative. There were no enlarged glands.

Second Admission

He returned October 2, 1928, with chills and fever, pain in gall-bladder region and arthritis. The fever alternated with chills and the temperature rose daily to 101° or 103°, the pulse going to 110 or more. Toward the last the daily temperature curve was typical of septicemia.

Physical examination showed pyorrhea, a heavy coating of tongue, and slight jaundice. The glands still were not enlarged. Six weeks before death the patient began to cough. Crackling râles were present in the lungs. Ten days before death a definite bronchopneumonia developed. The pain in the upper abdomen was almost unbearable. The patient died December 14, 1928.

The treatment throughout was symptomatic. Several blood transfusions were

made Potassium iodide was given for four weeks without improvement

Blood examination on the second admission (10-2-28) showed red blood cells, 3,170,000, white bloods cells, 11,000, hemoglobin, 80%, Sahli, polymorphonuclears, 75%, lymphocytes, 22%, large mononuclears, 3%

The final blood examination, made on 12-5-28, gave red blood cells, 2,900,000, white blood cells, 14,500, hemoglobin, 64%, polymorphonuclears, 86.5%, lymphocytes, 9%, large mononuclears, 4.5%, eosinophiles, 0, in 200 cells

The urine was negative The icterus in-

dex, 36 units bilirubin The Widal test, *B abortus* and *B tularensis* agglutinations were negative The Wassermann and Kahn tests were negative. The sputum was negative for tubercle bacilli

The X-ray verified the arthritis and diffuse infiltration of the lungs

Clinical Diagnoses Chronic cholecystitis, arthritis, septicemia due to undetermined cause, icterus, terminal bronchopneumonia and myocarditis

Abstract of Protocol

The body was that of an emaciated male 170 cm in length The skin and sclerae



FIG 1 Left lung showing Hodgkin's disease nodules and diffuse organizing pneumonia near base

were distinctly yellow. All of the upper teeth and several of the lower ones were absent. Those remaining were in poor condition. The tongue was heavily furred. There were no skin lesions and no superficial glandular enlargements.

Pericardium The pericardial sac contained 100 cc of bloody fluid. A firm band of adhesions connected the apex of the heart to the parietal pericardium, and there was an area of acute fibrinous exudate on the epicardium.

Heart Weight 490 Gm. The cavities and valvular orifices were negative, the coronary arteries were sclerosed, one branch of the left coronary being completely obliterated. The myocardium was white and fibrous.

Left Lung Weight, 355 Gm. The upper lobe was not remarkable. In the lower lobe

there were two kinds of nodules, varying in size up to a diameter of 2 cm. Two of the larger ones appeared to be calcified tubercles. The other nodules were numerous and had no distinct borders. Some were firm, white and tinged with red. Others were hard, white, and had excavated centers containing a thick creamy exudate. The lung tissue between the nodules was dry, air containing, and appeared normal. The bronchi were moist, reddened and some contained muco-pus. The peribronchial lymph nodes were enlarged to about 2.5 cm in diameter, were grayish white in color, and resembled nodes infiltrated by tumor growth.

Right Lung Weight, 510 Gm. Nodules similar to those in the left lung were present in all three lobes. In the lower lobe was a small area of diffuse consolidation 5 by 3 by 2 cm, and scattered areas of



FIG 2 Smear from active culture of monilia, showing mycelial and budding forms
Oil immersion

bronchopneumonia There were also collapse of the posterior portion of the upper lobe and compensatory emphysema of the apex The bronchi and nodes resembled those of the left lung

Gastrointestinal tract There was an acute inflammation of the duodenum and edema of the papilla of Vater The rest of the gastrointestinal tract was negative

Liver Weight, 1590 Gm In general the liver presented the picture of chronic passive congestion with moderate bile stasis There were three firm white irregular nodules with sharply scalloped borders and reddened margins The largest was 2 cm. in diameter and had a cartilage-like center The gall bladder was distended with thick, sticky, mucoid, reddish-green bile The mucosa was injected, edematous and inflamed No stones were present

Spleen Weight, 295 Gm It measured

17 by 9 by 4.5 cm The capsule was thin and tightly stretched Pale blotches were apparent beneath it On section the pulp was a deep, purple color with many creamy white spots

Kidneys Both kidneys presented the picture of chronic arteriosclerotic nephritis with retention cysts The right contained a healing infarct near the upper pole

The mesenteric and retroperitoneal nodes were somewhat enlarged, white, firm, and infiltrated

The pancreas, adrenals, prostate, bladder, and testes were negative

The head was reserved The joints were not opened

Principal Diagnosis General granulomatosis of uncertain cause

Additional Diagnoses Acute fibrinous pericarditis with effusion, old pericarditis with adhesions, healed infarct of myocardium



FIG 3 Smear made from a mixture of *monilia* and blood The *monilia* take the nuclear stains The preparation shows the difficulty of differentiation between the *monilia* spores and the nuclei of the leukocytes The resemblance made the demonstration of *monilia* in tissues particularly difficult

um, collapse of right lung with compensatory emphysema, chronic adhesive pleuritis, healed tuberculosis, multiple infarcts of spleen with enlargement, chronic passive congestion of liver, chronic cholecystitis and cholangitis, chronic nephritis, adenomatous hyperplasia of the prostate, general icterus, enlargement of joints

Post Mortem Bacteriological Report

Cultures were made at autopsy from the heart blood, pericardial fluid, bile, spleen, lungs and peribronchial nodes. All cultures yielded a heavy growth of *B. coli*. Large organisms, apparently mycelial forms of a fungus, could be seen in the cultures from heart blood, spleen, pericardium and peribronchial lymph nodes. After two weeks' incubation the colon bacilli died out and the fungus which proved to be a strain of *monilia* was isolated in pure cultures.

The *monilia* colonies were white and glis-

tening. When less than 24 hours old short arboreal processes extended from the colony. On microscopic examination these processes consisted of branching mycelia with oval spores forming at the ends and nodes. Smears of older colonies revealed only spores with occasionally a shadowy or skeletal remnant of a mycelium. All forms were Gram positive and showed no structural features except an irregular concentration of the nuclear material in some of the spores.

In broth this organism grew with slight granular turbidity which generally settled to the bottom. Acid was produced in dextrose and maltose broth. Lactose, saccharose, mannite and salicin were not affected. It did not give the characteristic yeast odor in broth or upon potato.

Large doses of culture administered intravenously were fatal for rabbits. Subcutaneous inoculation in rabbits and guinea pigs produced abscesses.

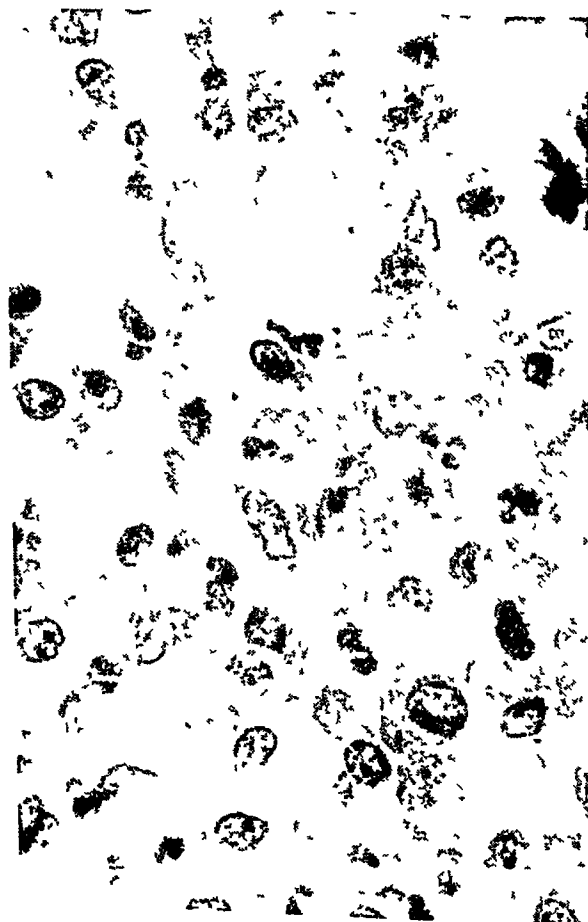


FIG 4 Photograph to show *monilia* in lung nodule. Note the group of *monilia* just above the center of the field. These *monilia* stood out as red bodies with pyronin and light green.

Diagnosis Monilia (species not determined)

Microscopic Findings

Heart The myocardium showed fibrous myocarditis

Lungs The lung sections showed a diffuse purulent exudate throughout the bronchi and bronchioles. They contained many bacteria and some larger irregular forms resembling monilia. The large cells to be described in the nodules were also seen in the alveolar walls at some distance from the nodules. There were a few areas of organizing pneumonia not associated with nodules.

Several sections of the lung contained well defined nodules, which were discrete, situated beneath the pleura. The margins were sharp and without limiting membranes. The alveoli in the advancing margins of the nodules were filled with fibrinous exudate and were often found lying next to normal

air sacs. In the affected areas all structures including bronchioles, blood vessels and alveolar spaces were destroyed by the granulomatous process. Apparently the reaction consisted of a primary fibrinous exudate which spread at the borders and organized at the centers. A typical nodule included one or more small bronchioles in which the epithelium was partially thrown off and partially swollen and adherent. The bronchial submucosa was infiltrated with an exudate of polymorphonuclear leucocytes. Toward the centers of the nodules, all normal landmarks were lost and the mass was made up of interlacing strands of fibrin, newly formed fibroblasts, fibrils, capillaries, infiltrating cells and broken bits of monilia. The monilia were differentiated with difficulty. They were not acid fast. They stained blue with phloxine-methylene blue and with the Gram-Weigert method. In both instances they took the fibrin and



FIG 5 Photograph of lung showing bronchiole filled with leukocytes and alveoli filled with fibrin undergoing organization

nuclear stains and could not be differentiated with certainty. By means of Giemsa's stain they could be differentiated from fibrin but not from nuclear particles. At the suggestion of Dr. Baldwin Lucké, pyronin and light green were used and a moderate number of red staining bodies which were morphologically monilia were found distributed throughout the lung lesions and bronchioles.

The kinds and relative numbers of inflammatory cells in the nodules varied considerably from field to field. Polymorphonuclear cells were diffusely distributed. Lymphocytes, plasma cells and large mononuclear phagocytes were very common and were the predominating cells in some areas. Some of them contained phagocytosed ovoid monilia, often two or three to a cell. Typical phagocytic foreign body giant cells with from three to ten or more nuclei were numerous and widely distributed. The unusual feature was the presence of many large cells which appeared to be identical with the "Dorothy Reed" cell of Hodgkin's disease. These were large cells with pink cytoplasm, irregular borders, vacuolated nu-

clei, which often had multiple nucleoli. Some of the cells were in mitosis and some had more than one nucleus. Some of these cells resembled megakaryocytes of the bone marrow.

Liver In several sections there were portions of nodules, which were identical with those found in Hodgkin's disease.

Spleen In general the spleen showed congestion with areas of red cells. The white granulomatous areas were essentially infarcts, with borders which were not sharply defined. "Dorothy Reed" cells were numerous in the pulp. Golden pigment-bearing cells and foreign body giant cells completed the picture.

Kidneys A moderate degree of arteriosclerotic nephritis was present, and one section had an infarct in the later stages of healing. The sclerosis was of the Monckeberg type.

Lymph Nodes The lymph nodes were replaced by fibrous tissue and presented the usual picture of Hodgkin's disease. The lymph follicles and normal arrangement of the nodes were lost. In some parts the

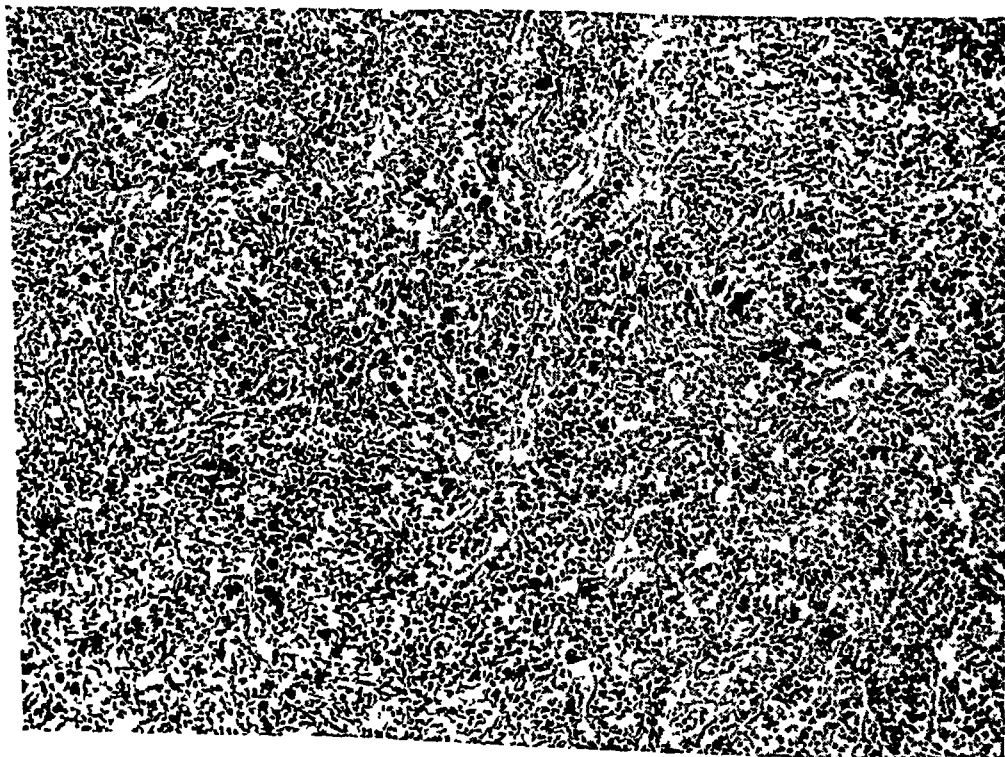


FIG 6 Photograph of peribronchial lymph node, presenting the picture of the sarcomatous form of Hodgkin's disease. Note the large cells, fibrosis, and absence of germ centers.

fibrous bands were wide and made up of many collagen fibrils which separated the gland into irregular alveolar spaces, filled with cells. The greatest number of cells were lymphocytes with large, deeply staining nuclei. Among them were many large cells with clear protoplasm, large cart wheel-like nuclei and one or more large nucleoli. Mitotic figures in these cells were numerous. Some were mononuclear and some had two or more nuclei. There was also a fair number of multinucleated giant cells of the foreign body type which presented typical, dark, evenly stained nuclei. In the peribronchial nodes, the giant cells often contained carbon pigment, while large cells which resembled the "Dorothy Reed" cells did not. Spore-like *monilia* bodies were found.

The pancreas, aorta, adrenals, and other organs showed no lesions attributable to *monilia*.

EXPERIMENTAL LESIONS

Animal inoculations were made to prove the pathogenicity of the *monilia*.

The intravenous injection of rabbits with pure cultures produced death within twenty-four hours. No microscopic studies of this group were made. Rabbits and guinea pigs were inoculated subcutaneously and intraperitoneally. In a week or ten days this group showed abscesses at the site of inoculation and *monilia* were recovered culturally and were demonstrated in the sections with pyronin and light green stains. In animals allowed to live for longer periods the abscesses healed by becoming surrounded by mononuclear leucocytes of the foam-cell type and by encapsulation. Finally, foreign body granulomas were formed containing giant cells filled with mycelial bodies and ovoid forms. Cultures were placed in the nostrils of anesthetized guinea pigs and a diffuse bronchitis

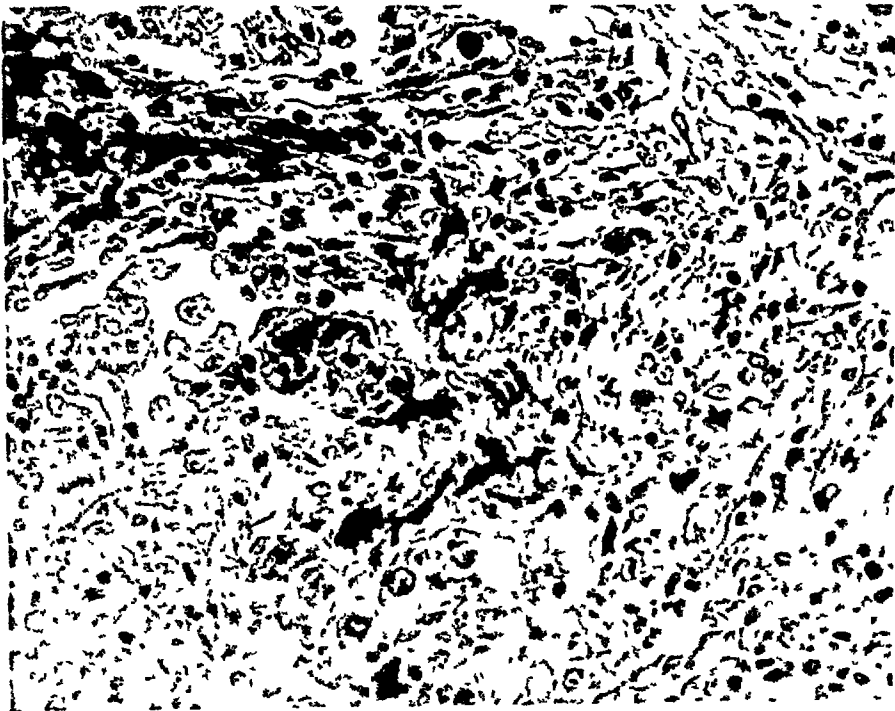


FIG 7 Higher power photograph of lung to show mononuclear cell type of exudate in nodule. A cell resembling a "Dorothy Reed" cell is present in the right center near the top. The dark staining masses were at first believed to be *monilia* but took the bluish green stain with Unna's pyronin and light green, showing that they were fibrin.

produced. Several of these animals died within two weeks.

SUMMARY AND DISCUSSION OF POINTS FOR AND AGAINST HODGKIN'S DISEASE

A Clinical Findings The clinical course indicated some unusual condition other than Hodgkin's disease or some overshadowing concurrent infection. Against Hodgkin's disease were the following points. The patient was in his seventy-first year which is far beyond the average age of Hodgkin's disease. Cases have been reported up to the age of seventy-six but the usual age is between twenty and forty and cases over fifty are rare. There were no superficial glandular enlargements. The symptoms and signs pointed to cholecystitis, arthritis, both of which were present, and to some chronic progressive granulomatous lesion in the lungs accompanied by chills and fever. The lung symptoms coincided closely with the reports of pulmonary moniliasis in the tropics and particularly resembled that condition as described by Farrah¹ among tea tasters in Ceylon. References to the reports of sixty-nine instances of pulmonary moniliasis in the United States were found in the literature since 1915. The fever in our case was of the septic type and was higher than that usually found in Hodgkin's disease. The blood picture was atypical. A secondary anemia did develop in the later stages though the continued leukocytosis of about 17,000 with a relative polymorphonuclear leukocytosis of 86.5 per cent and an absence of eosinophils favored acute infection. The patient was under observation for arthritis for six months

and was in the hospital for the last ten weeks of his life where he was seen daily by various members of the staff, all experienced in Hodgkin's disease, further, unusually complete laboratory work was done without anyone even so much as considering Hodgkin's disease as a possibility.

B Bacterial Findings The organisms recovered are not known to be associated with Hodgkin's disease. *B. coli* and monilia were isolated from the lungs, peribronchial lymph nodes and blood stream. *B. coli* was considered to be a secondary invader. Monilia were unique as an autopsy finding in our experience. They resembled *M. psilosis* though they were not considered identical. There was a heavy fur upon the tongue which could have been the source of a general terminal distribution, though we do not think this likely. We found gram-positive structures in the lung lesions and in some of the bronchioles away from the nodules which we believed to be monilia. The monilia were pathogenic for rats, guinea pigs and rabbits in which they produced chronic abscesses. Smears and cultures of these abscesses were regularly positive for monilia though they could be demonstrated only with the greatest difficulty in the sections, because their morphology, size, and staining reactions varied widely. We considered the monilia the responsible agents for the inflammatory part of the lung lesions, and for the acute lesions in the spleen, but only an accidental association with Hodgkin's disease.

C. Pathologic Findings The pathologic findings were not characteristic and were confusing. The diagno-

sis of Hodgkin's disease rested on the microscopic changes in the peribronchial nodes and upon the presence of "Dorothy Reed" cells in the lesions of the other organs. In typical Hodgkin's disease the lungs may escape entirely, but in this instance the lesions of the lungs were the outstanding pathological features and included organizing pneumonia, acute and chronic bronchitis, as well as the nodules. Inflammatory changes in the spleen were far more acute than typical Hodgkin's nodules. The question arose as to whether the case was a general moniliasis, Hodgkin's disease, or a combination of the two.

Sections were sent to several laboratories and the opinions of various pathologists were not wholly in agreement. Two reported "Hodgkin's sarcoma." Three reported Hodgkin's disease with unusual inflammatory reactions in the lung not typical of Hodgkin's disease. One said that the lymph node lesions would probably be diagnosed Hodgkin's disease in most laboratories, but that the lung lesions could be accounted for on a purely inflammatory basis. Another made a diagnosis of Hodgkin's disease, though he qualified the statement in that he had

seen the same large cells in avian tuberculosis and believed them to be megakaryocytes. One said that the large cells were present in a case of moniliasis of bone which he had studied.

After the demonstration of the monilia-like bodies in the lungs and spleen by means of the pyronin and light green stains, we made the final diagnosis as it appears in the title of this report.

CONCLUSION

A case of early Hodgkin's disease is described which appeared to be secondarily infected with a strain of pathogenic monilia. The reaction in the infected areas, as well as the Hodgkin's nodules contained the typical "Dorothy Reed" cells.

This finding suggested that these cells are wandering cells which may respond to inflammatory stimuli outside of the Hodgkin's nodules, just as other wandering cells and blood elements are capable of doing.

REFERENCE

- ¹FARAH, N. Observations on Castellani's bronchomoniliasis, with report of a case with pneumonic onset and a peculiar clinical aspect, Jr Trop Med, 1923, xxvi, 1-5.

Spotted Fever Immunization:

Results and Recommendations*

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CONSEQUENT upon a widening area of distribution and upon the increasing population within the areas that have become endemically affected, the spotted fever of the Rocky Mountains has become of enhancing importance as a public health problem^{218, 223} Of this fact, cognisance has been taken by state and local health officers, by regional and inter-state conferences, by private practitioners, and by the increasing co-operation of the Federal Government. The cooperation of the latter has taken the form chiefly of conducting epidemiologic and ecologic studies in the field, of carrying out laboratory investigations on the virus, and of the manufacture, in annually increasing quantities, of a preventive vaccine of proven, and we might add, great value^{209, 225}

The vaccine, as originated by R. R. Spencer and R. R. Parker has an important place in any control program, but is particularly necessary for use in localities where tick control measures can not be conducted economically, due either to the character of the terrain, the sparseness of the population, or the very occasional character of the menace from spotted fever Where, however, it has been found profitable to maintain tick control procedures, there is not yet justification

for diminishing the tick control activities because of the recent introduction of a preventive vaccine²²⁴

This paper will be limited to a study of the production, distribution, and efficacy of the spotted fever vaccine as originated by R. R. Spencer and R. R. Parker, the value of the vaccine as compared with other spotted fever control measures being given only incidental consideration inasmuch as this aspect has lately been elsewhere considered in detail by the author.²⁸¹

The need for a preventive serum or vaccine was early apparent in the study of possible prophylactic measures against spotted fever, as the disease is of great economic importance in the areas where it is most prevalent; as also in areas where it is of (consistently) great virulence^{36, 47, 97} P. G. Hennemann and J. J. Moore^{76, 84} attacked the problem from the aspect of passive immunity They showed that passive immunization offered virtually no prospect for effective prevention or therapy It was H. T. Ricketts^{49, 56, 75} and associates^{61, 69}, and later Noguchi^{142, 143, 144} who conducted the first studies on active immunization against spotted fever Subsequent studies of related nature were reported by Conner^{147, 148}, by Breinl¹⁶³, by Kuczynski¹⁰⁸, and by Otto¹⁷⁷ It was not, however, until the experiments of R. R. Spencer and R.

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R Parker resulted in the production of an attenuated virus, in sufficient concentration, that a practical vaccine became available^{150,153}. This vaccine was first released for distribution in 1925

THE NATURE OF THE VACCINE

The vaccine is the spotted fever virus obtained from infected ticks ("tick virus") rather than from the blood of infected animals ("blood virus"), its virulency is attenuated by chemical means. It is standardized for approximate potency by biologic (guinea pig) assay. Each dose (2 c c) equals the attenuation of approximately 20,000 minimum infectious doses for a guinea pig. Two such doses at five day intervals have constituted the standard course, which requires being repeated annually.

Although most vaccines are prepared by heating the organisms to 56° C it has been found necessary to obtain attenuation by means of a chemical, as the protective quality of spotted fever virus is entirely destroyed at the temperature of 56° C.

Manufacture of the Vaccine

Wild adult ticks, collected in the field, are permitted to feed on infected guinea pigs after the onset of the fever, placing about 75 ticks in a wire gauze capsule fastened to each animal. After two days of feeding the ticks are removed and placed at room temperature over moist sand, where they may be kept for several months. Before being used for making vaccine these ticks are again fed, this time on normal animals, for five or six days. This second feeding produces a tremendous increase in the number of minimal infectious doses of the virus per tick. For routine purposes it is not necessary to determine this dosage by the graded injections of the live tick-virus suspensions, as was formerly done.

The partly engorged ticks (male and female) are now ground in a mechanically

operated porcelain mortar and pestle with fine quartz sand and a small quantity of physiological salt solution which contains 16 per cent phenol and 0.4 per cent formalin. After thorough grinding the whole mass is transferred to a large stock bottle, and an additional amount of the salt solution and preservative is added until the concentration reaches, but does not exceed, four ticks per cubic centimeter. After standing for 48 hours, during which time the preservatives will precipitate most of the protein, an equal volume of physiological salt solution is added. This dilutes the preservatives to 0.8 per cent phenol and 0.2 per cent formalin. At this stage the material is kept for seven days at room temperature. This has been found a sufficient period to kill most extraneous organisms, including sporebearers.

The suspension is then diluted once more by again adding an equal volume of salt solution. This final dilution will contain 0.4 per cent phenol, 0.1 per cent formalin, and the killed virus equivalent of one tick per cubic centimeter. The sand, chitin, and precipitated protein is now removed by centrifugation and the remaining clear amber-colored supernatant fluid is ready for the final containers. Occasionally some precipitate forms afterwards. This can be disregarded for it does no harm when injected and besides has protective value. In fact, the discarded heavy precipitates from potent lots may be combined and resuspended in sterile salt solution, again cleared by centrifugation, and the clear supernatant fluid still found to possess high protective value. A number of such lots have been so made and used in human vaccination¹⁵².

Test for Potency and Sterility. Each lot is tested for potency by inoculating six guinea pigs subcutaneously with one cubic centimeter each. After twelve days the animals are given intraperitoneally a test dose of one cubic centimeter of guinea pig blood virus. If four of the six animals or more show symptoms of spotted fever the vaccine is considered suitable for human use. An arbitrary standard of potency is not adopted, it admits the operation of several factors. The potency of any lot is only approximately stated.

Sterility tests are made on each lot.

with the hygienic laboratory procedure for biologic products

Keeping Quality The vaccine is fairly stable at ice box and room temperature. Ice box preserved vaccine protected guinea pigs invariably up to 200 days and 6 out of 9 pigs at 576 to 597 days. Vaccine kept at room temperature protected 8 of 9 pigs up to 108 days and one-half of 10 pigs at 215 days, the remainder dying of spotted fever

DISTRIBUTION OF THE VACCINE

The vaccine is produced solely by the U. S. Public Health Service at Hamilton, Montana. It is distributed to physicians without charge and it is expected that only a nominal charge will be made for administering the vaccine. Application for the vaccine should be made to the Officer in Charge, U. S. Public Health Service, Hamilton, Montana.

Each year there has been an increasing demand for the vaccine. The heaviest calls are from Montana, Wyoming, Idaho, and Oregon, the last named state using the most in 1930. There is a moderate demand from South Dakota, Nebraska, Colorado, Nevada, and Washington.

The amounts that have been distributed are as follows

Year	C C	Number of Doses	Number of Courses
1925	372	186	93
1926	3,412	1,706	856
1927	6,284	3,064*	1,532
1928	6,500	3,250	1,625
1929	16,600	7,786	3,893
1930	32,000	16,000	8,000
1931	64,000	32,000	16,000

*Includes 312 doses at 25 c c per dose

METHOD OF ADMINISTRATION

Equally good protection has been effected by the subcutaneous, intravenous, intramuscular, and intraperito-

neal routes, the latter employed in guinea pigs only. Ordinarily the vaccine is administered subcutaneously. Attempts to vaccinate animals by forcing them to swallow the vaccine have produced immunity in only a few instances, and failed in the great majority of cases.

REACTIONS

Less than five per cent of four thousand persons have complained of constitutional symptoms. These have included malaise, slight fever, nausea, and aching joints or muscles. Protein reactions with urticaria and edema have occurred in about one per cent of those vaccinated, the symptoms usually appearing very shortly or within a few hours after the injection, but in one instance were delayed ten days. The symptoms last from a few hours to several days, but in one man the urticarial rash persisted somewhat for nine months, finally disappearing following infection with spotted fever. About one-half of those who have reacted after the first injection do not do so on subsequent injections, whereas a few react more violently. Marked collapse occurred in one person who, the next day, felt normal except for weakness.²⁰¹

Local reactions have mostly been inconsequential and limited usually to local redness, swelling and itching about the site of injection. Swelling sometimes extends below the elbow and occasionally to the hand. Itching, the most common complaint, either disappears or becomes scarcely noticeable in persons who have been vaccinated several times.

DURATION OF IMMUNITY

Data from the Bitter Root Valley test indicate that the duration of pro-

tection in the average individual does not exceed one tick season. The period varies in individuals, however, and for some may be quite short. Vaccination annually is therefore desirable.

While effective immunity does not last longer than one year, there is evidence that a residual immunity persists for a much longer time.

POPULATIONS IMMUNIZED

Immunization has included the vaccination of three accurately controlled experimental groups, and a dispersive, not accurately controlled distribution of the vaccine. The general distribution, not available for accurate comparative statistics, was as follows:

In	No of Individuals to Jan 1, 1930	No of Individuals to Jan 1, 1932 (Approximately)
Montana (excluding Bitter Root Valley test group)	401	2,600
(including test group)	(3,231)	(7,100)
Idaho (excluding test group)	203	1,400
(including test group)	(396)	(1,593)
Wyoming	863	2,900
Oregon	30	3,300
Nevada	5	300
Colorado	3	275
Utah, Dakotas and Nebraska	2	275
Washington and Cali- fornia	0	250
General distribution	1,507	8,300
Total distribution	4,530	16,000

The three test or controlled groups were the following: the U S Public Health Service workers (including state control employees), the Idaho Test Group, and the Bitter Root Valley Test Group. The Idaho Test

Group included 94 persons in 1926 and 99 in 1927 (none thereafter), a second annual vaccination not being offered in 1927 to those vaccinated in 1926. The number of inoculations administered to the Public Health Service (including state control) employees is included in the following statistics concerning the Bitter Root Valley Group.

The following table (table I) shows the number of individuals who, in each year, had received the number of vaccinations and revaccinations as indicated by the integers on the course line.

TABLE I

COURSES RECEIVED	1	2	3	4	5	6	7	TOTAL
1925	34							34
1926	624	30						654
1927	846	339	112					1,296
1928	1,469	430	141	11				2,051
1929	2,067	491	191	71	10			2,830
1930	2,550	555	257	143	64	9		3,578
1931*	2,720	800	550	265	150	10	5	4,500

*Estimate by the author, official records not yet compiled for publication.

RESULTS

From the results of a two year test (1926 and 1927) made in southern Idaho (Snake River Valley) against the mildest type of the disease, and another test against the most virulent type, which has been in progress for seven years in the Bitter Root Valley, the following conclusions are justified—that against the milder types of infection the vaccine usually affords full or nearly full protection, while against the highly virulent type the degree of protection is usually sufficient to cause a marked amelioration of the customary very severe symptoms, and to predispose to the recovery of most cases.

In southern Idaho infection is very prevalent among persons handling

sheep on the range, and the test was therefore confined to that industry. During the two seasons of 1926 and 1927, 193 sheep herders were vaccinated, and 364 non-immunes served as controls. A single case only occurred among the vaccinated men (1 in 193). This man had refused the second injection. Among the 364 control individuals there were 22 cases, or one in every 16.55 men.

The Bitter Root Valley case mortality for the twelve years, 1917 to 1928, was 53 deaths out of 69 cases, a rate of 76.81 per cent. In six of these twelve years the mortality for adults was 100 per cent. During the period of the four years under consideration (1925-1929) there were, including the non-vaccinated control group, a total of 18 cases with 15 deaths, a case mortality rate of 83.3 per cent, among the non-vaccinated persons living in the Bitter Root Valley.

The results of the test against the malignant Bitter Root Valley strain yield the following statistics for the period 1925 to 1931, inclusive.

	Vaccinated Group	Non-vaccinated, Control Group
Number of individuals in group	3,578	about 8,700
Approximate ratio to whole population	30%	70%
Number of cases in group	16	30
Case incidence	1/223*	1/290
Died	2	22
Death rate	12.5%	73.32%
(Parker-Spencer series)	9.09%	90.91%

*The slightly greater incidence rate in the vaccinated group was due to the fact that vaccination was first carried out to proportionately greater degree in a "well defined

A composition of the Public Health Service (Group A) cases, seven in number (with one death), the Bitter Root Valley cases, 16 in number (with two deaths) and the experience of Dr. E. L. Jewell with two cases (both recovered) each with the equally fatal Kirby Creek strain of spotted fever, gives a total of only three deaths in twenty-five cases of almost fatal virulency, a mortality rate of 12 per cent against the twelve year average of 85 per cent.

Parker and Spencer, writing of their initial series, have been able to say "Considering only adult cases in the Bitter Root Valley as a whole, the recovery of 10 of 11 vaccinated adults, 7 of Group A and 4 of Group B (90.91 per cent recovery) during the four year test period offers vivid contrast, first with the death of 10 of 11 non-vaccinated adults (90.91 per cent mortality) during the same period, and second, with death of 9 of every 11 non-vaccinated adult cases (84.91 per cent mortality) during the past twelve years."²⁰¹

PROSPECTS

Having passed the experimental stage, the prospects for the adequate employment of the vaccine have to do

dangerous zone on the west side of the valley", where of 1,208 persons, 496 were vaccinated, letting the remainder, 712 in number, serve as controls. Considering only the group of 1208 in the dangerous zone on the west side of the valley, there were during the four years (1926-1929) three cases (1 in 165) among the members of the vaccinated group, none of which was fatal, while there were nine cases (1 in 79) among the non-vaccinated group, seven of which proved fatal, a case mortality rate of 77.7 per cent.

with problems of distribution, and of coordinating the use of the vaccine with other control measures, according to the relative economic positions of the measures available. Maximum distribution requires suitable publicity and organization of distributing channels—matters of routine.

The evaluation of the vaccine's economic position is not definitely established, there appearing to be a tendency to undervalue it (compared with other measures) even by those reasonably conversant with the situation. This we believe is a great mistake.

The limited supply, the high cost of manufacture, the disposition of many persons to refuse to submit to any sort of vaccination, the necessity for annual reinoculations, and the popular appeal of other more visibly tangible control measures, such as tick destruction and rodent destruction, all serve to restrict the use of the vaccine to a greater degree than they should.

While it is evident that other control measures can not be diminished the slightest, in areas of great malignancy or tick concentration, on account of the introduction of the vaccine, the great fallibility of these measures renders imperative the systematic use of the vaccine in all dangerous areas, despite the additional cost. In areas of lesser danger the use of the vaccine is equally imperative, as in most such localities the liberal use of tick destruction and rodent destruction measures are economically infeasible. Particularly requiring the vaccine are transient visitors to dangerous areas, and residents of remote or sparsely settled localities in the infected areas. It is particularly the latter class of persons

that present serious problems in the matter of distribution.

In final analysis it is apparent that the prospects for the use of the vaccine are predominately in the hands of the medical men serving in the localities affected, if they energetically sponsor the use of the vaccine they will be supported by the proper persons for obtaining the necessary publicity, if they are negligent the popular appeal will eventually foster an increasing use of the vaccine, but never perhaps to a sufficient degree unless actively supported by the medical profession. Certainly, however, there is no reason to infer that physicians will be remiss in this matter, as the initial response of the profession has been exceedingly gratifying. Nevertheless, to facilitate distribution, various regional organizations and standards need to be created, these are matters of administration, largely being developed at the present time, and will be dealt with as recommendations.

RECOMMENDATIONS

Current problems have to do with methods of manufacture and standardization, means of distribution, educational programs, and plans of inoculation.

The progressively increasing demand for the vaccine will undoubtedly be met adequately by the U. S. Public Health Service for years to come. It may, however, become necessary to require some reallocations in the manner of defraying the cost of manufacture, as the production of the vaccine is exceptionally costly due to the high labor charge for field work in obtaining the ticks and for the laboratory work.

needed to infect them and rear them. Methods of manufacture are, however, being studied from the aspect of reducing unit cost and of increasing potency. A better method for assaying and standardizing potency is desirable.

Distribution through the medical profession should continue as the main avenue of release. In controlled areas and other highly malignant localities, the vaccination should be under the immediate supervision of the statistician in charge. For reaching men on remote sheep ranges, the state sheep inspectors, veterinarians, and other intelligent persons of the locality should be trained to give the vaccine and to keep the records.

As maximum distribution can not be obtained without persistent publicity of the proper sort, it is recommended that newspaper editors, ministers, school teachers, district supervisors, and educators in the higher grades be officially requested to publish the facts concerning spotted fever vaccination, and to give such information of local interest as will facilitate obtaining the inoculations. For this publicity the school and civic exercises of Washington's birthday should be utilized systematically to the end that the date of February 22 shall become firmly associated in the public mind with the need for obtaining the first of the year's spotted fever inoculations. Similarly in areas of great malignancy the same custom should also become identified with May Day, May 1st, for the single mid-season injection. On the other hand, in areas where one injection of the year is the optimum dosage, this fact should be made known to relieve the public mind and to dis-

courage the needless waste of the vaccine.

Regarding dosage and plan of administration, in view of the need of economy and maximum general efficiency, it is recognized that collectively better results will be obtained by so employing the vaccine as to depart from the present standard dosage (two injections of 2 c c each, at five day intervals) wherever local requirements, particularly the greater or less local virulency of the disease, indicate the advisability of establishing an optimum dosage for the locality concerned. Thus a single mid-season injection (about May 1st) in addition to two pre-season injections, is decidedly to be recommended for persons exposed in areas of great malignancy. On the other hand, in certain localities a single annual injection of 2.5 c c, before the commencement of the tick season, should be considered optimal, according to local conditions. In areas of intermediate virulence the optimum dosage appears to consist of two injections of 2 c c each, or possibly the first of 1.5 c c and the second of 2.5 c c, the interval of five days being permissibly lengthened to seven days where local conditions seem to make the latter interval more feasible.

Regarding organization of the distributing channels it is recommendable that state health boards shall (to assist them and the Federal authorities) appoint non-salaried, resident district supervisors among the regular medical practitioners of their State, with view to surveying local requirements, obtaining and supervising proper publicity, keeping records, rendering reports, and otherwise assisting in the

distribution of the vaccine, with consideration to apportioning it where it is most needed

SUMMARY

Six years' experience with the Spencer-Parker spotted fever vaccine, a chemically attenuated form of the virus, has demonstrated it, by several controlled experiments, to be of great and dependable value in preventing the occurrence of the mild type of spotted fever, and of great value in mitigating the severity of the highly fatal type of the disease, the mortality of the latter being reduced from the twelve year average of eighty-five per cent to approximately ten per cent (nine to twelve per cent)

As the protective action of the vaccine lasts only one season (four to twelve months), annual reinoculations are necessary before the commencement of each tick season. Since the introduction of the vaccine in 1925 to the year 1931, inclusive, between 25,000 and 30,000 persons have been vaccinat-

ed, and many of them revaccinated annually from two to six times

The demonstrated value of the vaccine, and the great need for it in endemic areas, has created an increasing demand for it from the medical profession and the laity, a demand that will continue to be met gratis by the U S Public Health Service Laboratory at Helena, Montana, despite unusual difficulties of manufacture and distribution

While it is recognized that tick destruction and rodent control measures can not be safely diminished on account of the introduction of the vaccine, it is of great importance that the vaccine be used adequately and systematically in all endemic areas, as in most areas it is the only preventive measure available that is both dependable and economically feasible. To effect better distribution and economy, several recommendations are made concerning organization, publicity, and modification of dosage with respect to local requirements, according to the virulency of the local strain.

BIBLIOGRAPHY

- ³⁰RICKETTS, H T. A summary of investigations of the nature and means of transmission of Rocky Mountain spotted fever, *Trans Chicago Path Soc*, 1907, vii, 73-82
- ⁴⁷RICKETTS, H T. Recent studies of Rocky Mountain spotted fever in Montana and Idaho, *Med Sentinel*, 1908, xvi, 688-697
- ⁴⁸TUTTLE, T D. Indications for state control of Rocky Mountain tick fever, *Med Sentinel*, 1908, xvi, 697, 704
- ⁴⁹RICKETTS, H T, and GOMEZ, L. Studies on immunity in Rocky Mountain spotted fever, *Jr Infect Dis*, 1908, i, 221-244
- ⁵⁰RICKETTS, H T. Some aspects of Rocky Mountain spotted fever as shown by recent investigations, *Med Rec*, 1909, lxxvi, 843-855
- ⁵¹GOMEZ, L. Spotted fever in the rabbit, *Jr Infect Dis*, 1909, vi, 383-386
- ⁵²DAVIS, B F, and PETERSON, W F. Complement deviation in Rocky Mountain spotted fever, *Jr Infect Dis*, 1911, viii, 330-338
- ⁵³DAVIS, B F. Unfinished experiments of Dr. Howard T. Ricketts on Rocky Mountain spotted fever. In *Contrib to Med Sci by H T Ricketts*, Univ of Chicago 1911 409-418
- ⁵⁴HINEMANN, P J, and MOORE, J I. The production and coagulation of serum for Rocky Mountain spotted

- fever Preliminary note, Jr Am Med Assoc, 1911, lvii, 198
- ⁸⁴HEINEMANN, P J, and MOORE, J J Experimental therapy of Rocky Mountain spotted fever, Jr Infect Dis., 1912, x, 294-304
- ⁹⁷FRICKS, L D Rocky Mountain spotted fever A report of laboratory investigations of the virus, Pub Health Rep, U S Pub Health Serv, 1916, xxxi, 516-521
- ¹⁴²NOGUCHI, H Prophylactic inoculation against Rocky Mountain spotted fever, Sp Bull No 26, Montana St Bd Health, 1923, 44-47
- ¹⁴³NOGUCHI, H Immunity studies of Rocky Mountain spotted fever, Jr Exper Med, 1923, xxxvii, 383-394, xxxviii, 605-626
- ¹⁴⁴NOGUCHI, H Experimental prophylactic inoculation against Rocky Mountain spotted fever, Northwest Med, 1923, xxii, 301-303
- ¹⁴⁷CONNER, C L Quantitative peculiarities of mixtures of the virus and immune serum of Rocky Mountain spotted fever, Jr Med Research, 1924, xlv, 317-328
- ¹⁴⁸CONNER, C L Immunity in Rocky Mountain spotted fever, Jr Immunol, 1924, ix, 269-289
- ¹⁵⁰SPENCER, R R, and PARKER, R R Experimental studies on tick virus, U S Pub Health Rep, 1924, xxxix, 3027-3040
- ¹⁵³SPENCER, R R, and PARKER, R R Vaccination of monkeys and man, U S Pub Health Rep, 1925, xl, 2159-2167
- ¹⁶³BREINI, F Untersuchungen uber die Immunitat bei Rocky Mountain spotted fever, Ztschr f Immunitatsforsch, 1926, xli, 123-136
- ¹⁶⁶KUCZYNSKI, M H, and BRANDT, ELIZABETH Neue ätiologische und pathogenetische Untersuchungen in der "Rickettsiengruppe" (Fleckfieber und der Rocky Mountain Spotted Fever), Krankheitsforschung, 1926, iii, 26-74
- ¹⁷⁷OTTO, R Fleckfieber und amerikanisches Felsengebirgsfieber, Centrbl f. Bakteriologie, etc, Abt Orig, 1928, v, 106, 279-291.
- ¹⁹⁰SPENCER, R R, and PARKER, R R Improved method of manufacture of the vaccine and a study of its properties, Hygienic Lab Bull No 154, Wash, D C, 1930, Pp 63-72
- ²⁰¹PARKER, R. R, and SPENCER, R R Results of four years human vaccination, Hygienic Lab Bull No 154, Wash, D C, 1930, Pp 72-103
- ²⁰⁵WEIGL, R Behavior of virus of Rocky Mountain spotted fever in body of mouse Comp rend. de soc de biol, 1930, ciii, 823-826
- ²⁰⁹PARKER, R R Present status of the use of public health vaccine for Rocky Mountain spotted fever, Eighth Bien Rep Montana St Bd Entomol, 1931, Pp 36-38
- ²¹⁸DYER, R E, BADGER, L F, and RUMREICH, A Rocky Mountain spotted fever (eastern type) Transmission by the American dog tick (*Dermacentor variabilis*), U S Pub Health Rep, 1931, xlvi, 1403-1413
- ²²³KEMP, HARDY A, and GRIGSBY, C M The occurrence and identification of an infection of the Rocky Mountain spotted fever type in Texas, Texas State Jr Med, 1931, xxviii, 395-398
- ²²⁵SPENCER, R R Expansion of investigation on tick borne diseases by the U S Public Health Service Pub Health Rep, 1931, vlvi, 2097-2101
- ²³¹TOOMEY, NOXON Control of the tick borne diseases, methods and economics, ANN INT MED, 1932, v

Gastric Secretion—The Electrolytes before and Their Changes at Various Periods after Histamine Stimulation*†

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INTRODUCTION

THE institution of hypodermic injections of histamine as a gastric stimulant, has enabled investigators to obtain undiluted gastric juice with much more facility than previously, no corrections have to be made for dilution by an alcohol meal.

Gamble and McIver¹ determined the amount of fixed base in a Pavlov pouch from the fundic end of the stomach. They found a fairly constant level of Cl^1 but a varying amount of base. The level was low on a meal diet, and high on a fasting stomach. The gastric Cl^1 value (158 c.c. 0.1 N per 100 c.c.) is near the total fixed base concentration in blood plasma.

In a series of interesting and well-controlled experiments MacLean and Griffiths² showed that the introduction of acetic acid, hydrochloric acid, and sodium acid sulphate into the stomach will prevent the secretion of hydrochloric acid until enough neutral chloride has been secreted to dilute the

gastric contents to 0.2 per cent hydrochloric acid or below. Then hydrochloric acid is secreted. The total chloride soon reaches a level (0.11-0.12 N) and remains so, as if "the combined efforts of emptying and secreting tend to adjust the concentration of Cl^1 to a normal maximum level of 0.11-0.12 N". They believe that "secretion of HCl by the gastric glands is a self-limiting process and after its duty is fulfilled the chlorine is kept level by the secretion through the gastric glands of neutral chlorides".

MacLean and Griffiths³ were also able to show that dogs having a Pavlov pouch behave in regard to hydrochloric acid and chloride secretion in exactly the same way as normal man: an initial rise in acid then a fall and concomitantly an increase in neutral chlorides, also, that the total chloride in the pouches remains about constant during secretion. They feel that their work definitely rules out the theory of alkalinization of gastric juice by duodenal regurgitation which was advanced by Boldreff⁴ in 1915.

In a former experiment, these same investigators⁵ determined, by a very delicate method, the amount of CO_2 and dioxide in various specimens of gastric

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juice Only when bile was present were they able to demonstrate an increased amount of carbon dioxide Furthermore, the hydrochloric acid curve showed the normal rise and fall whether carbon dioxide was present or absent

On single test specimens of gastric juice, the total bases, the total chlorides, the free hydrochloric acid, and the phosphates were determined by Bulger, Stroud and Heideman⁶ The fasting juice was compared with the secretion stimulated by drink (400 c c of water containing 1 c c of phenol-sulphonphthalein solution) In this way the dilution was corrected The authors showed that very little change occurred in the total chlorides, but that during secretion the total base fell in proportion to the increase of acid. They believe that the chlorine ions and water leave the blood in about the same concentration as that found in the serum There appears to be a definite change in the phosphate content of the human gastric juice which is inversely proportional to the content of HCl Specimens with a phosphorus content as high as 11.17 mg per cent were found in cases of achlorhydria Gastric juice with a high HCl content averaged about 4.5 mg per cent of phosphorus

Polland, Roberts, and Bloomfield⁷ also studied the chloride, base and nitrogen curves before and after histamine stimulation They found that the increase in titratable acidity is due to the greater increase in output of chloride over base, also, that nitrogen is present, and that it varies in proportion to the base

In six cases of anacidity following

histamine stimulation, Bloomfield, Roberts and Polland⁸ found chlorides, bases, and nitrogen in the normal concentration. As the volume of secretion was quite low, the total amount of the substances was naturally much below the average normal

It seemed of interest to know whether more information could be added to these investigations, and furthermore to ascertain what changes, if any, took place in the blood and urine during the phases of gastric secretion This part of the investigation will be presented separately

METHOD

The one hundred and sixteen individuals investigated were in the great majority from the Gastro-intestinal Dispensary of the Johns Hopkins Hospital They presented a multiplicity of complaints and sicknesses and they represented a cross-section of the usual number of admissions. A few estimations were made on patients in the medical and surgical wards, these were selected cases Complete analyses were made on ninety of these 116 patients and the results are recorded below

The individuals to be investigated reported to the clinic after fasting for 15 hours A duodenal tube was passed and its position was seen, by fluoroscopy, to be just beyond the dependant portion of the stomach All patients were cautioned not to swallow saliva. After the removal of the entire fasting contents, each patient was given histamine (ergamine acid phosphate) hypodermically, 0.005 mg per pound of body weight Constant drainage was instituted and the total gastric

secretion was collected and separated into three one-half hour periods

The hydrogen ion concentration was determined by the colorimetric method, using Clark's standards and indicators.⁹ Titratable acidity was determined by the standard method using dimethyl-amino-azobenzene and phenolphthalein as indicators, a definite canary yellow color was taken as the endpoint of the former indicator and the first permanent pink as that of the latter. Total chlorides were determined by the method of Van Slyke,¹⁰ total bases by the method of Stadie and Ross,¹¹ inorganic orthophosphates by the method of Benedict and Theis,¹² CO₂ content by the method of Van Slyke and Cullen¹³ and trypsin by the author's method.¹⁴

OBSERVATIONS

For clearness of description the material has been divided as follows

- (a) Those individuals who secrete hydrochloric acid after histamine stimulation

Group I includes cases which contain free hydrochloric acid in the fasting or resting gastric juice. See table I.*

Group II includes cases which contain no free hydrochloric acid in the fasting juice. See table II.

- (b) Those individuals who secrete no hydrochloric acid before or after histamine stimulation

Group III includes cases which have a gastric juice with a pH between 3.0 and 8.0, the achlorhydrias. See table III.

*To facilitate reading, the figures, graphs and tables have been placed at the end of the article

Volume

The amount of resting or fasting juice varies within wide limits. Groups I and II from 0 to 190 cc, the achlorhydrias, Group III, from 0 to 95 cc. After histamine stimulation there was almost always a rapid production of gastric juice in the acid producing cases. The amount collected in comparable periods, however, varied within wide limits, the period in which the greatest amount was to be collected, could not be predicted, but usually the maximum was to be found in the first half-hour with decreasing amounts in the second and third. With the production of a large amount of material the consistency became quite limpid, clear and of high titratable acidity. There were cases, however, in which a high titratable acidity was associated with a small volume of thick, mucoid material.

In the cases of achlorhydria, it was quite unusual to collect large amounts. In fact, it was often difficult to obtain sufficient material for the complete analysis. During the various periods it was rare to obtain more than that found in the fasting juice.

Total Chlorides

Chlorides were found in the gastric juice of all patients investigated. The amounts varied within wide limits and in relation to the type of secretion.

The fasting juice of the 25 cases in Group I, hydrochloric acid in all specimens, contained total chlorides between the limits of 88 and 143 milliequivalents per liter, an average secretion of 110. Following histamine stimulation these cases had an increased content in all but four of the

cases, at times rising to a level of 150 to 158 meq,* with a general average of 127. Usually there was a slight decrease in amount towards the end of secretion. There was, however, much less variation in the chloride content than in the acidity as will be shown later.

The chloride content of the acid free fasting juice of the 21 individuals of Group II was found to be within lower limits, 58 to 113 meq and averaged 91. After histamine stimulation, an increase similar to that in the group above was noted and although at times the highest chloride content was equal to Group I, the general average was lower, 114 meq. Here the small increase in chlorides after stimulation in comparison to the corresponding acid rise was even more noticeable.

The chloride content of the fasting juice of the 44 cases in Group III who were unable to secrete free hydrochloric acid in any specimen, was found between the limits of 37 and 115 meq, with an average of 81. After stimulation, there was at times an increase and at other times a decrease in the chloride content, in an exceptional instance the amount rose from 108 to 138 meq, in many cases there was but little change.

The average amounts of the chlorides of the specimens of the three groups have been charted in figure 1 to show the amounts found before and after stimulation. The difference in the levels of the three curves is quite striking.

The cases of Group III, the achlorhydrias, have been separated into four

main subdivisions determined by clinical diagnosis. The subdivisions selected were organic disease of the stomach including carcinoma of the stomach and one case of questionable syphilis, marked nephritis with retention of non-protein nitrogen products, pernicious anemia, and benign achylia. These are shown in figure 2. A study of the figure reveals the following interesting points:

- 1 In the group of benign achlorhydrias, there is a general trend towards a high percentage of chlorides in the gastric juice. The only exceptions to this are Case no 125, an apparently healthy house officer, Case no 121, dementia praecox, and Case no 124, an old colored woman. In this group it is clearly seen that there was no fixation of secretion concentration of the salts.
- 2 The cases of pernicious anemia are able to secrete salts through a wide range of concentration.
- 3 In the severe nephritics the secretion of chlorides in the gastric juice is at the same high level noted in the benign achlorhydrias. The number of cases is too small to draw any conclusion from the small range of concentration strength from specimen to specimen.
- 4 The most important finding in the cases of organic disease is that the great majority of these cases secreted a gastric juice having a low salt content. It is also interesting to note that half of these patients were able to vary the chloride secretion concentration through as large a range as

*Hereafter meq is used as an abbreviation of milliequivalents per liter.

the majority of the benign achlorhydrias. The latter group, however, secreted at a higher level as noted above.

Acidity

Michaelis¹⁵ has shown that all the free hydrochloric acid of the gastric juice has been neutralized when the juice is titrated with alkalis to pH 2.9. This end-point may be recognized (when dimethyl-amino-azobenzene is used as the indicator) when a salmon pink color is reached. Titrating to a canary yellow color gives results a trifle too high but has been used as an end-point in this work as the difference is very small and the end-point much sharper than that encountered in titrating to salmon pink. Michaelis has further shown that beyond pH 3.0 the hydrogen ion concentration in N/10 HCl drops almost perpendicularly to pH 10. A change in this titration curve is due to the presence of acids other than free hydrochloric.

In the tables there are a few cases with a pH beyond 3.0 in which values from 2 to 10 are given under free hydrochloric acid. This is due to the fact that pH 4.0 (canary yellow color) was taken as the end-point for free hydrochloric acid titration.

The twenty-five cases of Group I secreted a fasting juice in which free hydrochloric acid varied from a small amount up to 94 meq. Following stimulation there was an increase of acid content in twenty cases, a few went up to 120 meq.

In Group II where HCl was secreted only after stimulation with histamine, the acid content occasionally rose to the high level of the first group, the

general average was much lower. The relationship between the total chlorides and acid content of all groups is shown in figure 1.

In Group II there were ten specimens which had an hydrogen ion concentration between 3.4 and 5.0 as may be seen by referring to table II, Cases no 10, 15, 16, 24, 25, 61, 64, 107, 118. The hydrogen ion concentration must be due to the presence of acids other than free HCl but at the present time it is impossible to do more than speculate on their nature.

The hydrogen ion concentration in the preponderant number of the achlorhydria cases was found to be about 7.0, if the pH was considerably greater, it is not to be accepted as quite correct since the escape of CO₂ will cause large errors.

In both of the groups secreting HCl there was a rise in acidity subsequent to the histamine stimulation and generally a decrease in the last, the 90 minute, specimen, and at times in the last two specimens. This observation has been made by numerous investigators and is mentioned here not as reiteration but because the interpretation of the diminution has been greatly discussed. A consideration of this point will be given later.

Bases

The change of secretion of total bases into the gastric juice presents an interesting series of phenomena. In Group I (patients who secreted HCl into all specimens) it was found that that amount of base varied inversely to the titratable acidity. In other words during the period of secretion there was a drop in the milliequiva-

lents of total base per liter, and towards the end there was a rise in all cases except nos 43, 54, 113, 116 and 118 where either the HCl or total chlorides did not fall. The amounts found in the fasting juice varied between 26 and 94 meq, the general average of total base was 67. After stimulation the average dropped to 53 meq and ranged between 30 and 84.

In Group II, those patients who secreted no free hydrochloric acid in the fasting juice but did after stimulation, the same phenomena were observed, only more intensified as there was often a very marked drop after stimulation. The total bases in the fasting juice varied between 60 and 120 meq, a general average of 97. After stimulation there was a marked drop to limits between 44 and 90 meq with an average of 66 meq.

In the achlorhydrias, Group III, there was much less change in total fixed base after histamine stimulation, the curve of secretion being almost a duplicate of that of the chlorides of the same group. Figure 3 gives a clear-cut illustration of the changes in the three groups and may be superimposed on figure 1. The total variation in total fixed base in all four periods for the 44 cases was from 34 to 132 meq. The general average for each period was as follows: Control 88 meq; 30 minutes, 88 meq; 60 minutes, 89 meq; 90 minutes, 95 meq.

It is important to note that some cases contained about the same number of milliequivalents of base throughout the periods of collection; i.e., if the fasting juice contained only 50 meq the specimens collected after histamine also contained about the

same number in contrast to the marked changes noted in Groups I and II. Likewise, if the fasting juice contained 100 meq or more the following specimens contained 100 meq more or less. There was an equal number of cases, however, who showed the ability to change secretion strength of bases. As was noted above, the same change occurred in the secretion strength of chlorides.

A very fair estimate of the changes in bases, which have been observed in the subdivisions of achlorhydrias, may be obtained by a reexamination of figure 2, since the figures for base agree more or less with those for the chlorides, although in individual instances it was seen that the total bases were several milliequivalents per liter higher than the corresponding amounts of chlorides per specimen. This very important inequality will be discussed further on.

Ortho-phosphates (Inorganic)

The estimation of inorganic phosphorus would seem to be of some importance since it is usually found in greater concentration than in the blood, except during periods of large volume output and relatively high acidity.

In Group I the limits of inorganic phosphate lie between 0.5 and 3.2 meq of phosphate ion in the resting juice. After histamine there was generally a decrease in the concentration and in cases with high volume output the level decreased, at times, to 0.3 meq.

In Group II the limits of the phosphate in the acid free resting juice lie between 1.1 and 5.4 meq, a substantially higher level than that noted for the resting juice of the preceding

group After stimulation there is usually a decrease in amount but as the volume and acidity of this group seldom reach the heights of Group I, it is rare to find a decrease equal to the limits of Group I

In Group III (achlorhydrias) the limits of the phosphate in the fasting specimen lie between 11 and 56 As with the chlorides and bases there is much less variation in the amount of phosphate of this group than in Groups I and II The level remained more or less constant throughout the period of observation This is illustrated in chart 1

Carbon Dioxide

In cases where the CO_2 content was estimated the gastric juice was collected under a thick covering of oil It is recognized that the method allows of only an approximate determination but even so it has been possible to account for several apparent inaccuracies in the acid-base ratio The CO_2 content as determined represents minimum values

A recheck of the amounts of CO_2 recovered in relation to the pH of the juice, permits the opinion that, within fairly rough limits, the results are of value The high CO_2 values were always found with cases having a pH beyond 7.0, and at times 8.0 This last figure can be obtained only by loss of CO_2 to the air, as has been said above

In cases in which hydrochloric acid was present in all specimens, Group I, the CO_2 content was usually between 1 and 4 volumes per cent

In the non-acid fasting specimens of Group II, there are unfortunately only five estimations Those specimens analyzed, however, have a CO_2

content of from 10.0 to 14.5 volumes per cent Some of these contained bile After stimulation the CO_2 assumed the same value as in Group I

The estimations made on Group III, the achlorhydrias, showed a general upward trend of CO_2 content, varying from 5.5 to 67.0 volumes per cent In a rough way the CO_2 content was proportional to the pH and had no direct relationship to bile or trypsin content

Trypsin

The measurement of trypsin represents the milligrams of non-protein nitrogen produced from 20 cc of 0.5 per cent casein in phosphate buffer of pH 7.5 by the action of 1 cc of a 1:10 dilution of gastric juice incubated for half an hour at 37.5° C

In Group I amounts varying from none to 4.0 mg have been found The few cases showing a biliary regurgitation have usually been found to have higher values but at times trypsin has been demonstrated in the absence of bile There may be a bile tinge to the gastric juice without any demonstrable trypsin

In Group II there was a marked increase in the amount of trypsin found in the acid free resting juice either with or without the presence of bile The largest amount found was 11.0 mg After histamine stimulation occasionally larger amounts were found than in the comparable specimens of Group I and occasionally trypsin disappeared with the secretion of gastric juice

The achlorhydrias as a group have much the greater content of trypsin, in fact amounts up to 18.0 mg. were not uncommon It was not entirely absent in any specimen but Case number

70 had very small amounts. and strangely enough this patient regurgitated bile

DISCUSSION

It is possible to correlate some of the data at hand and to give some interpretations

In the acid secreting cases a high volume of secretion was always associated with a high content of chloride and hydrochloric acid

As noted under volume the typical case runs its highest secretion during the early periods after stimulation and gradually decreases as the stimulation ceases. From figure 1 it has been possible to show that the same type of curve is also found in the chloride and the acid content of the successive periods. However, the volume, the total chloride and the acid content vary considerably from case to case, and some cases with small volume secretion will have a high chloride and acid content—this occurred in one case secreting a high mucus-like fluid

In chart 2 the relation of volume to total chlorides has been plotted. The achlorhydrias, it is here shown, secrete the chlorides at a lower level and associated with this there is generally a low volume

In chart 3 the relation of volume to acid content has been plotted. In order to be able to include the achlorhydrias, the free hydrochloric plus the so-called combined or total acidity was used. The value of the latter averaged about 10 meq. The same points as in chart 2 are illustrated, i.e., when there is a large volume of secretion, the acid content is high, but here there are some very noticeable exceptions in which a high acid

content is associated with a very low volume

In the specimens without free hydrochloric acid the volume is seen to fall generally below 40 c.c. and, in the large percentage, below 20 c.c. per thirty minute period. The estimation of the combined or total acids, i.e., those substances, acid or buffer, which hold the gastric juice below pH 3.0, has a certain value but it would be erroneous to consider the value as having the same relation to volume as has the estimation of hydrochloric acid.

Influence of Duodenal Regurgitation

It may be interesting to consider the data in regard to the influence of duodenal regurgitation on the regulation of the acidity. Figures 1 and 3, which have been presented to show the relationship between the various electrolytes, demonstrate the fact that in the acid secreting cases there is a normal rise and fall in the acid curve and that furthermore there is a smaller but yet, none the less, definite rise and fall in the secretion of chlorides. In accord with the theory of duodenal regurgitation, the fall in acid should be accomplished by regurgitated alkaline duodenal contents

In order to throw further light on the subject, specimens were examined for the presence of bile and of trypsin. These were noted to appear in a most irregular manner throughout the different periods of extraction. At times one or both of them were found when there was a diminution of acidity in the fourth specimen but as frequently they were not present. They were found not only when there was no decrease in the amount of acid but also when there was no increase in the

amount of the chlorides, making it even more unlikely that regurgitation would explain the changes of acidity.

It is certainly possible for the duodenal contents to diminish the amount of gastric acidity during the periods of collection or duration of normal digestion. This action is of secondary importance, however, as it has been shown that the fall in acidity takes place without its aid and that the amount and strength of hydrochloric acid decreased with the cessation of stimulation.

Amount of Electrolytes Secreted

Figure 4, for ease in comparison, presents the typical secretion of electrolytes of each of the three groups, and of a normal blood serum. The latter represents the findings in one of the cases in Group I, on whom serial blood and urine analyses were made at the time when the fasting specimen of gastric juice was taken. The value for protein is represented by the amount of base fixed by serum albumen and serum globulin at pH 7.35. The albumen-globulin ratio was taken as 1.8. Calculations were made by the formula of Van Slyke et al.¹⁶

$B \text{ protein} = 0.243 \text{ protein}$

The difference between the amount of base and the cation was considered to be due to organic acids.

Rôle of Bases and Bicarbonates

The secretion of base into the gastric juice is interesting. In those cases which have the ability to secrete hydrochloric acid there is a post-stimulation drop in the content of the base which is in inverse proportion to the increase in the content of acid. In these cases it has been shown that ex-

cept for an occasional slight difference (usually within the limit of experimental error) there is a mathematical equality between the determined cations (hydrogen and bases) and the anions (chloride and phosphate). In this relation the phosphate is usually so low that its presence may be disregarded. This agreement is shown clearly in figure 4, which illustrates the relation between base and hydrochloric or free acid with the changes in the chlorides.

The course of a typical case is demonstrated in figure 5. The fasting contents contained 10 meq of hydrogen ion (free HCl) and 75 meq of bases, this was almost exactly counterbalanced by the 83 meq of chloride. During the various phases of secretion this relationship between the anion and cation remained about the same although there was a decided increase in the milliequivalents secreted under the stimulation of histamine.

The relationship between the bases and chlorides in the group of achlorhydrias is shown in graph 5. It is demonstrated that although many of the amounts in the individual specimens are in close accord, there are others, rather numerous, which fall outside the limit of experimental error. This difference is found not only in cases of true achlorhydria but also in the acid-free resting juice of patients who secreted hydrochloric acid after histamine stimulation. See Cases no. 88, 95, 102, 112, etc.

In Case no. 95 which secreted acid after histamine stimulation the relationship between the anions and the cations of the acid-containing specimens was almost equal as is seen in figure 6. In the fasting juice of pH

70 the bases were greater than the chlorides by 15 meq. The carbon dioxide content of the specimen was 11 meq, and of the acid-containing specimens about 3 volumes per cent, too small an amount to be of significance.

A consideration of the achlorhydrias shows that the content of CO_2 plays an important rôle in equalizing the base and acid columns. Case no. 112 has been selected from a series of similar cases to illustrate this point in figure 7. There are, however, cases of achlorhydria from which but small amounts of CO_2 have been recovered. These are generally cases whose gastric juice has a pH below 7.0.

It is known that the CO_2 content of hepatic duct bile and pancreatic fluid is high and consequently it seems only reasonable that the regurgitation of these fluids into a nearly neutral gastric juice would result in the presence of CO_2 . In this series several of the specimens on which CO_2 determinations were made showed no evidence of bile and also the trypsin estimations were not unusually high. Consequently it seems quite definite that CO_2 is present in the achlorhydric gastric juice of human beings.

The Comparison of Total Chlorides of Gastric Juice and Blood Plasma

The amount of chlorides of the gastric juice in one case reached 158 meq, a considerably higher figure than that of the blood serum, although the sum of the blood serum bases is about equal to it. In the majority of cases the amount was much lower, making a general average for 46 cases of 120 meq of gastric juice chlorides. Therefore, although the milliequivalents per

liter of chlorides secreted were lower than the total number of anion or cation milliequivalents per liter of the blood, the chlorides of the gastric juice of the cases of Group I are almost always higher than those of the blood serum.

The acid free resting juice of patients who have the ability to secrete hydrochloric acid after histamine had an average of 91 meq of chloride, varying between the limits of 58 and 113. This may be compared with fasting and secretion juice of the true achlorhydrias in which there was a general average of 83 meq, varying between 37 and 115. In both of these groups the chloride level was always lower than the total milliequivalents per liter level of bases in the serum but sometimes was above and sometimes below the level of the serum chlorides.

The Secretion Concentration of Bases and Free Hydrochloric Acid

The point cited above naturally led to the question of the secretion concentration of the salts and acid found in the extracted gastric contents. The term *secretion concentration* is used to represent the concentration at which the salts and free hydrochloric acid are produced by the cells before dilution. The easier method of approach would seem to be by determination of the secretion concentration of salts in cases of achlorhydria and in the acid free resting juice of Group II.

- a To see if there was a marked difference in secretion concentration from case to case
- b To determine the changes, if any, which took place at various periods of analysis in the cases of achlorhydria

As a solution to the first problem

several cases have been collected into table V. The sixth column shows that in the acid free resting juice and in corresponding achlorhydria specimens there is a marked variation in the base content from case to case. When the total content, as determined, was reckoned as the equivalent quantity of sodium chloride (NaCl), the salt content so calculated approximated the actual salt content of the juice but did not include the Na_2HPO_4 and NaH_2PO_4 . Since there are no complicating factors such as a change in the chemical constituents of fluid, the concentration of salts in the extracted material represents their secretion concentration into the gastric juice. Furthermore, it must be kept in mind that this fluid is a different fluid from that which appears with the acid secretion in which there is a change in the chemical constituents. Consequently within the limits set in the above argument there is considerable variation in the secretion concentration of salts into the unstimulated acid-free, and the achlorhydria, stomachs.

The secretion concentrations in the former group varied from 333 to 650 mg per cent. In the stimulated and unstimulated gastric juice of the achlorhydrias, the variation was even more pronounced, namely from 225 to 794 mg per cent.

The solution of the second problem, as far as the cases of achlorhydria are concerned, is equally simple and the results may likewise be seen in table V. There was always some, and frequently much change. In one of the cases of pernicious anemia, an initial fasting secretion concentration of 232 mg per cent was increased to 637 mg per cent after histamine stimula-

tion. Case no 44 is of some interest because hydrochloric acid appeared only in the 60 minute specimen. The salt concentration in the fasting juice was 510 mg per cent, changing to 435 mg per cent in the specimen collected for 30 minutes after stimulation.

Another group of these cases, however, showed but little variation in secretion concentration from specimen to specimen. It has been impossible to make any satisfactory classification for diagnosis on the basis of stationary or changing levels of secretion concentration after stimulation.

The determination of the secretion concentration of the salts in the acid secreting cases is not simple because the question of the influence of other molecules such as HCl in varying quantities is to be considered. This in turn brings up several points about the secretion of the hydrochloric acid which would be interesting to solve.

- a Is it secreted at different concentrations in different individuals?
- b Is it secreted at different concentrations at various phases of secretion in the same individual?
- c When the secretion of hydrochloric acid takes place does the stomach secrete salts at the pre-stimulation level or does it secrete them at higher or lower levels?

Before these questions can be answered, a few ideas must be explained.

With the production of acid there is always an increase in the content of chlorides but this increase is insufficient in amount to account for all the hydrochloric acid. This inequality is compensated for by a drop in the amount of base, as has been seen in figures 1 and 3. This decrease in

have nothing to do with the secretion of base and be only a result of dilution by hydrochloric acid in the presence of an increasing or decreasing salt secretion, either in respect to amount or to concentration

As an essential point in this theory of secretion it is necessary to admit of two types of cells: one group secreting hydrochloric acid in pure solution; the other secreting the various bases as salts (chiefly as chlorides). The anatomical arrangements of the organ and its physiology makes it rather difficult to promulgate another belief. This is especially true in consideration of the secretion concentration of salts in the cases of achlorhydria.

The method for the determination of the secretion concentration is as follows. In Case no 98, there were 45 cc of gastric juice extracted as fasting secretion. This contained of base, 85 milliequivalents per liter; acid, 10 milliequivalents per liter; phosphate, 0.8 milliequivalent per liter; and total chloride, 75 milliequivalents per liter. Due to its small amount, phosphate may be left out of the reckoning. Base has been calculated as NaCl with a molecular weight of 58, and therefore a milliequivalent or 1 cc. contains 0.058 gms NaCl. The molecular weight of HCl has been calculated as 36 and a milliequivalent as containing 0.036 grams HCl.

The amount of free HCl in 45 cc
10 milliequivalents per liter
 0.1×45

But $10 \text{ meq HCl} + 75 \text{ meq NaCl} = 85 \text{ meq}$
And HCl represents

Therefore

And X, the grams HCl in 100 cc
But

$$\begin{aligned} &= 0.1 \text{ milliequivalents per cc} \\ &= 45 \text{ milliequivalents free HCl in} \\ &\quad 45 \text{ cc} \\ &= 0.162 \text{ grams free HCl in 45 cc} \end{aligned}$$

$$\frac{10}{85} = .1176 \text{ milliequivalents secreted}$$

$$1176 \times 45 = 529 \text{ volume of secretion of pure HCl necessary to produce the quantity found in total volume of gastric juice}$$

$$\begin{aligned} 529 \quad 0.162 &= 100 \quad X \\ X &= \frac{100 \times 0.162}{529} \\ &= 306 \text{ grams} \end{aligned}$$

And therefore HCl as secreted by the acid producing cells before dilution

But since
and
and

Therefore X, the grams of HCl in 100 cc or the secretion concentration of HCl as secreted by the acid producing cells before dilution, is by interpolation as follows

$$\begin{aligned} X &= \frac{100 \times 0.162}{45 \times .1176} = \frac{100}{45} \times \frac{0.162}{.1176} \\ &= \frac{100}{45} \times \frac{45 \times 0.036 \times 0.1}{10/85} \\ &= \frac{100}{45} \times \frac{45 \times 0.036 \times 0.1 \times 85}{10} \\ &= 10 \times 0.036 \times 85 \\ &= 0.10 \times 0.036 \times \text{number of milliequivalents of total chlorides in the specimen} \end{aligned}$$

The same formula may be used in estimating the secretion concentration of sodium chloride by substituting 0.58 for 0.036

It has already been shown that in the cases of achlorhydria and in the acid free resting juice of patients who secrete free hydrochloric after histamine the secretion concentration of sodium chlorides (bases calculated as NaCl) is subject to wide variation, not only from patient to patient, but in successive samples taken before and after histamine stimulation in the same patient. By the use of the formula just explained, it has been possible to bring to light several interesting observations on acid containing specimens

- (1) Hydrochloric acid was secreted at varying concentrations between the limits of 316 to 564 mg per cent. This applied to all the specimens from the 46 acid secreting patients of Group I and Group II.

During the period of observation on the average patient (before and after histamine stimulation) there was a change in the secretion concentration of hydrochloric acid. It was lowest in the fasting specimen and rose to its highest level during the height of stimulation, usually to fall somewhat towards the end of stimulation. With the diminution of secretion concentration there was also a decrease in volume of free hydrochloric acid. In other words the concentration of the pure hydrochloric acid solution as secreted followed a curve similar to that of the secretion of the determined total chlorides as in figure 1.

- (2) Sodium chloride was secreted at varying concentrations between the limits of 510 and 916 mg per cent. This also applied to all the specimens of Groups I and II.

That which was true of the variation of secretion concentration of free hydrochloric acid in individual cases, is true also of sodium chloride. The lowest secretion concentration was generally found in the resting specimen and the highest during the height of stimulation to fall off slightly towards the end of secretion. In one important manner there was a lack of parallelism to the free hydrochloric acid secretion concentration towards the end of stimulation there was a fall in the volume of hydrochloric acid secreted. This was not so markedly reflected in the salts since usually the post-stimulation volume of secretion of salt solution remained at the same content for some time. The secretion concentration of base calculated as NaCl varied directly as the secretion of the determined chlorides. This is as true of the achlorhydrias as of the acid secreting cases.

The increase in the percentage concentration of hydrochloric acid in the extracted material is, therefore, due to two factors (a) the increased volume output of hydrochloric acid produced by the stimulation of the acid secreting cells and (b) to the increased con-

centration of the acid produced by the cells at the height of stimulation

The diminution found in the concentration of salts in the successively extracted acid containing specimens is also due to two factors (a) Although the volume of salt solution secreted may be somewhat increased, the volume secreted is relatively small in comparison to the volume of acid solution secreted. The figures for this statement are included in table V (b) If the salt secretion strength had continued at the prestimulation level the concentration in the extracted materials would have been still lower as is seen in table V, therefore, its ultimate content could only have been produced by increase in secretion strength

CONCLUSIONS

Neutral salts, phosphates, and CO_2 are normally secreted into the resting stomach. There is no constant strength at which the CO_2 and the salts are secreted as they vary markedly in different patients. Hydrochloric acid may or may not be found in the resting juice, its presence probably represents a different physiologic process than that represented by the resting state.

Histamine provokes an increased secretion of gastric juice into most stomachs. It is probably normally accompanied by the secretion of hydrochloric acid. A large volume of secretion was always accompanied by free acid. It seems that acid is secreted throughout the duration of the stimulation and that as the stimulus wears off the production of acid ceases, and

the secretion returns to its resting state. The volume of secretion tends to run a course parallel to the acid. Variations, which may be pathologic, have been noted from this statement and qualifications have been listed above. As the amount of acid increases there is an increase in the secretion concentration, this is also true within the restrictions noted above.

The secretion of the neutral salts continues during the period of stimulation and increases in secretion concentration parallel with the acid. On the other hand the volume output is considerably less than that of hydrochloric acid and a diminishing percentage content of the neutral salts is found in the extracted material in contrast to the increasing percentage of hydrochloric acid. As the stimulus to secretion wears off the production of hydrochloric acid ceases. The volume of salt solution secreted by the cells also diminishes but evidently the concentration of the salt solution continues at a more elevated level for a varying period of time.

Phosphates diminish in concentration in the extracted juice during the successive half-hour periods of observation.

CO_2 is not found in the juice containing free hydrochloric acid but appears in amounts related to the pH of the achlorhydria juice.

The gastric mucosa of many achlorhydrias still retains the ability to secrete salts at various concentrations although for some unknown reason the ability to secrete hydrochloric acid is lost.

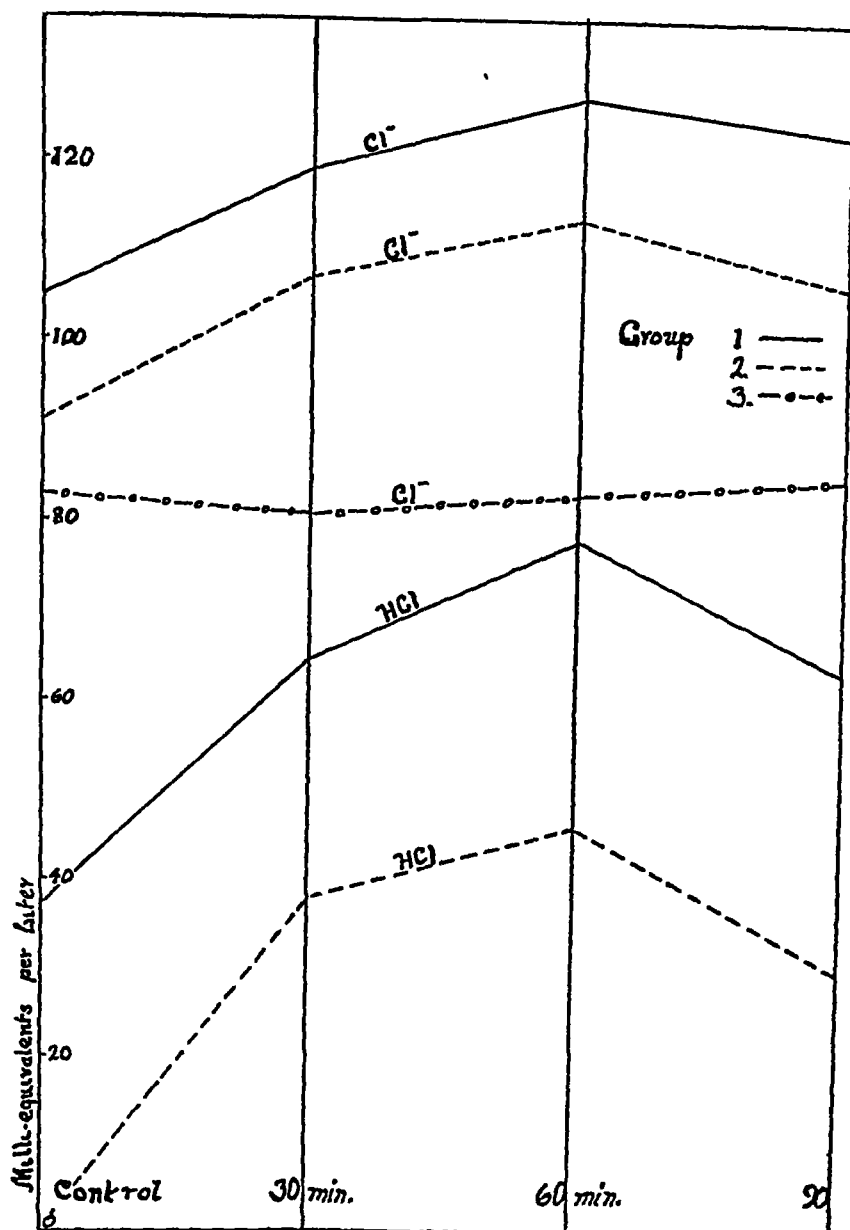


FIG 1 Composite chart of total chlorides and free hydrochloric acid in Groups I, II and III. Variations before and after histamine stimulation as averaged from 20 or more cases per group.

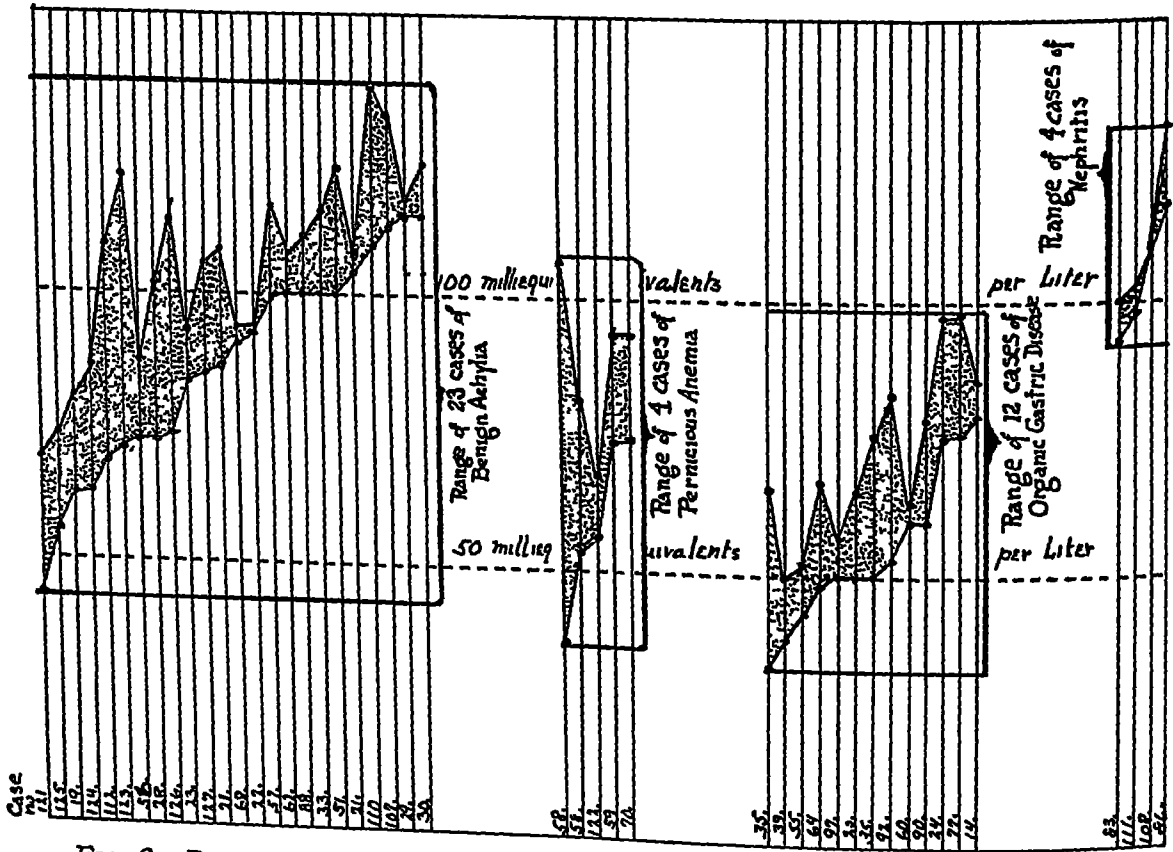


FIG 2 Range before and after histamine stimulation of total chlorides per case of achlorhydria, grouped according to diagnosis

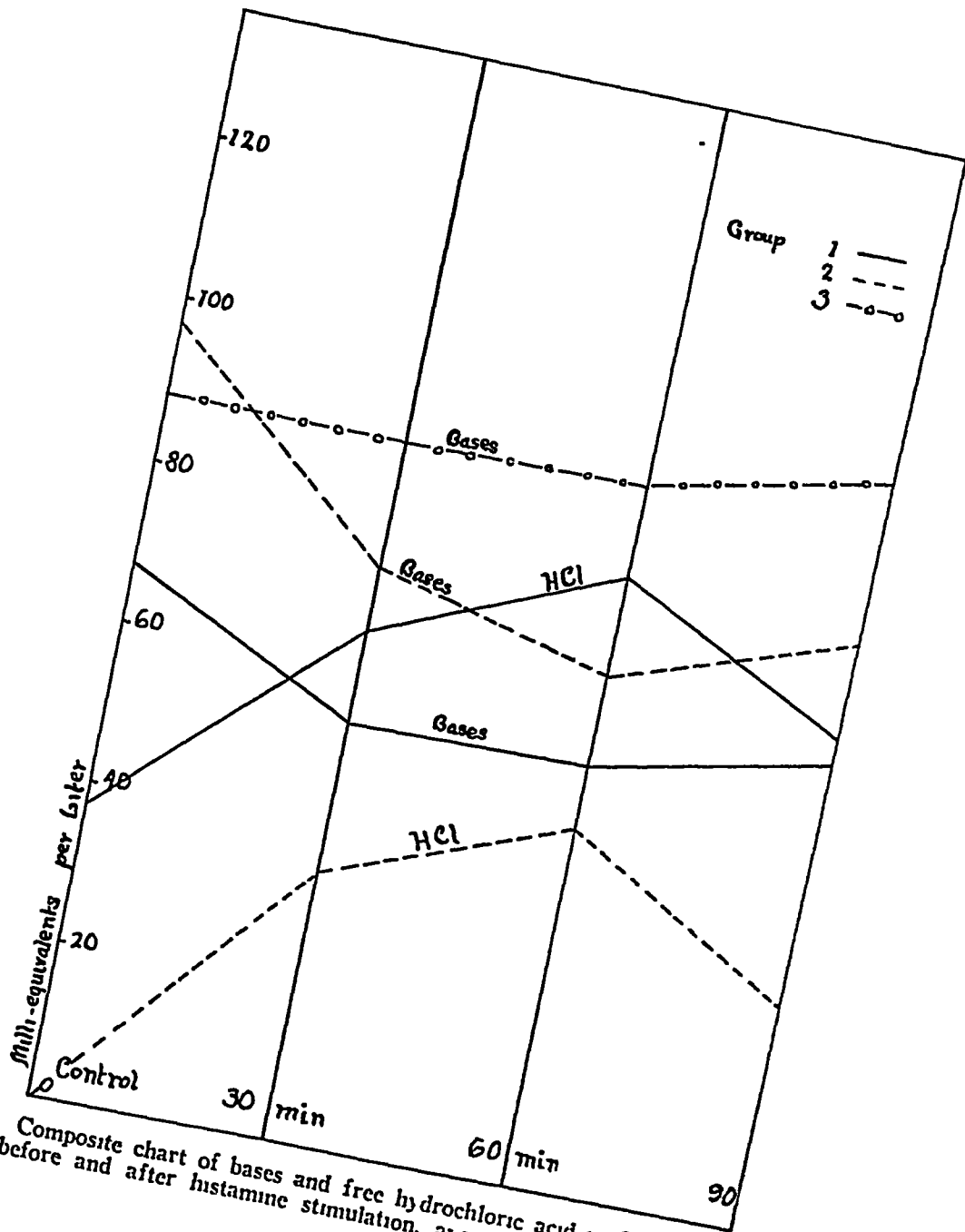


FIG 3 Composite chart of bases and free hydrochloric acid in Groups I II and III Variations before and after histamine stimulation, averaged from 20 or more cases per group

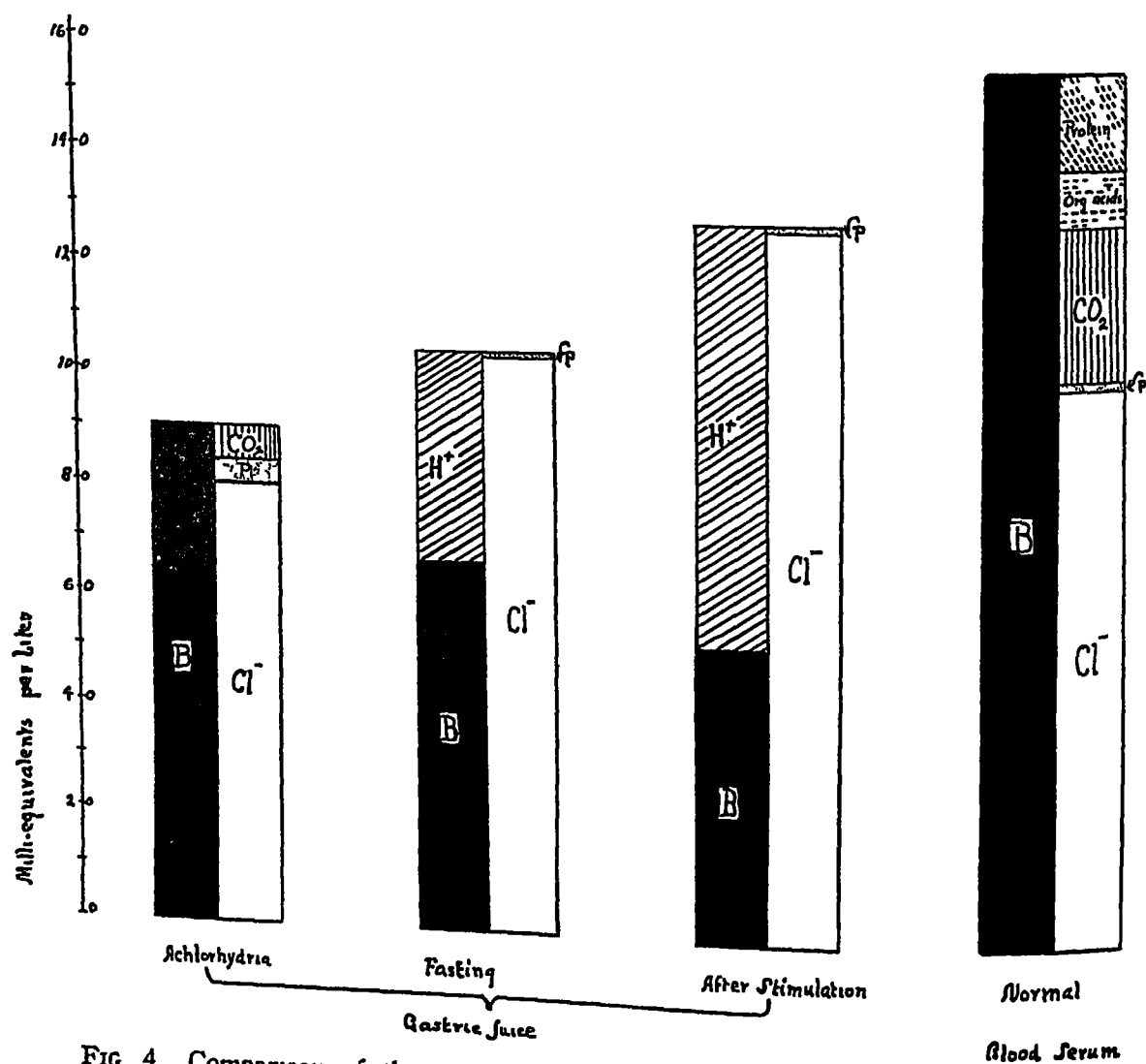


FIG 4 Comparison of the total electrolytic content of typical specimens of gastric juice with the electrolytic content of normal blood serum

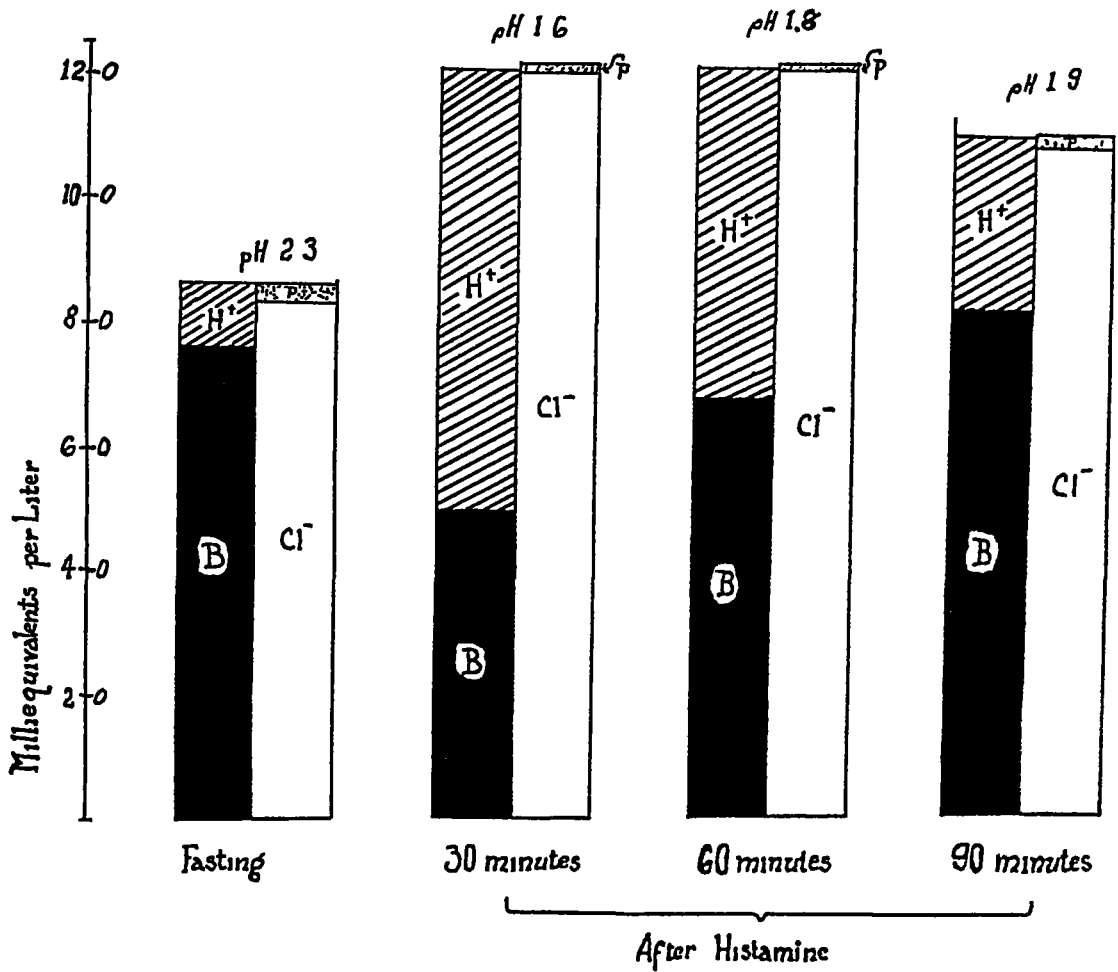


FIG 5 Typical normal case of Group I showing electrolytic changes during histamine stimulation

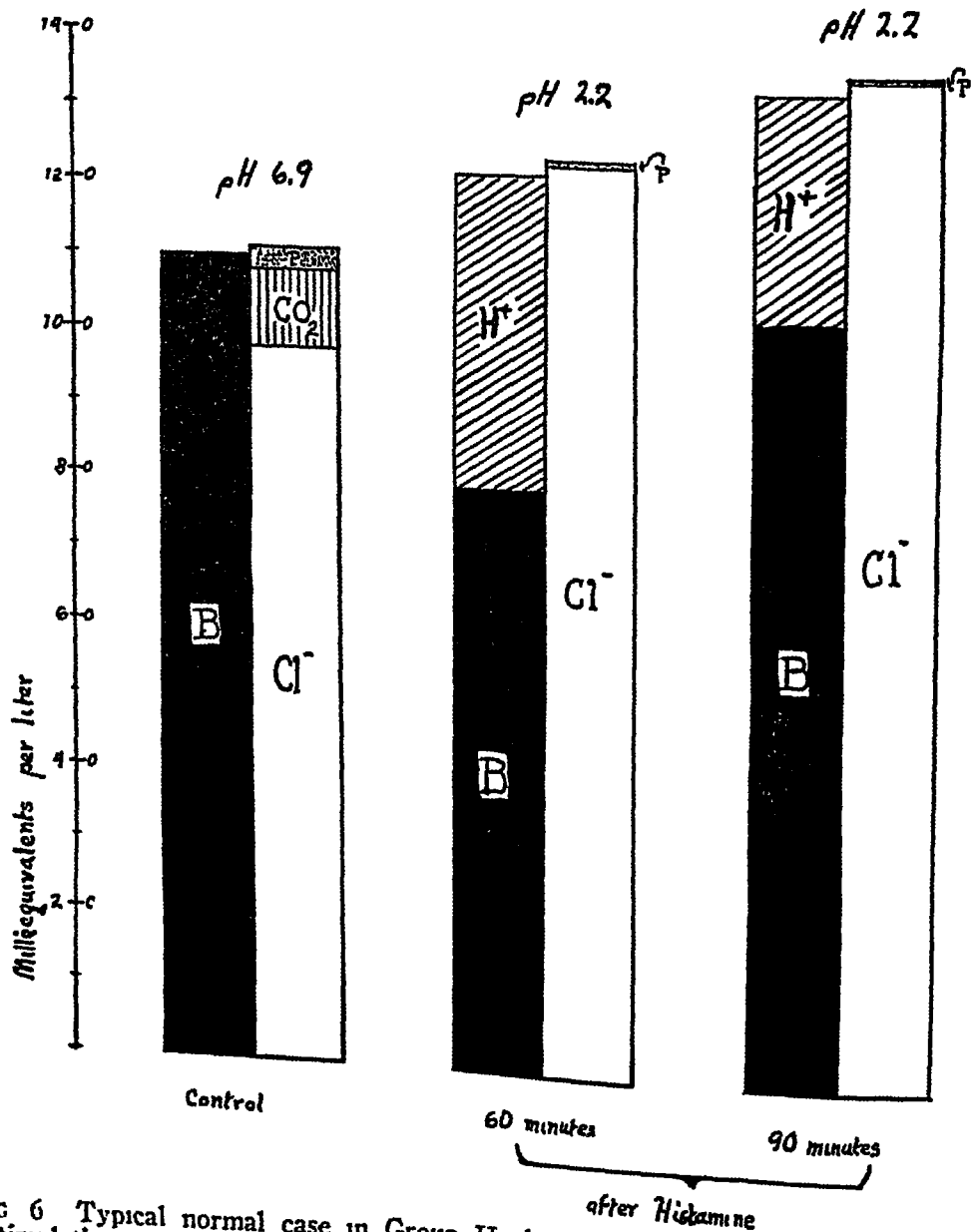


FIG 6 Typical normal case in Group II showing electrolytic changes during histamine stimulation

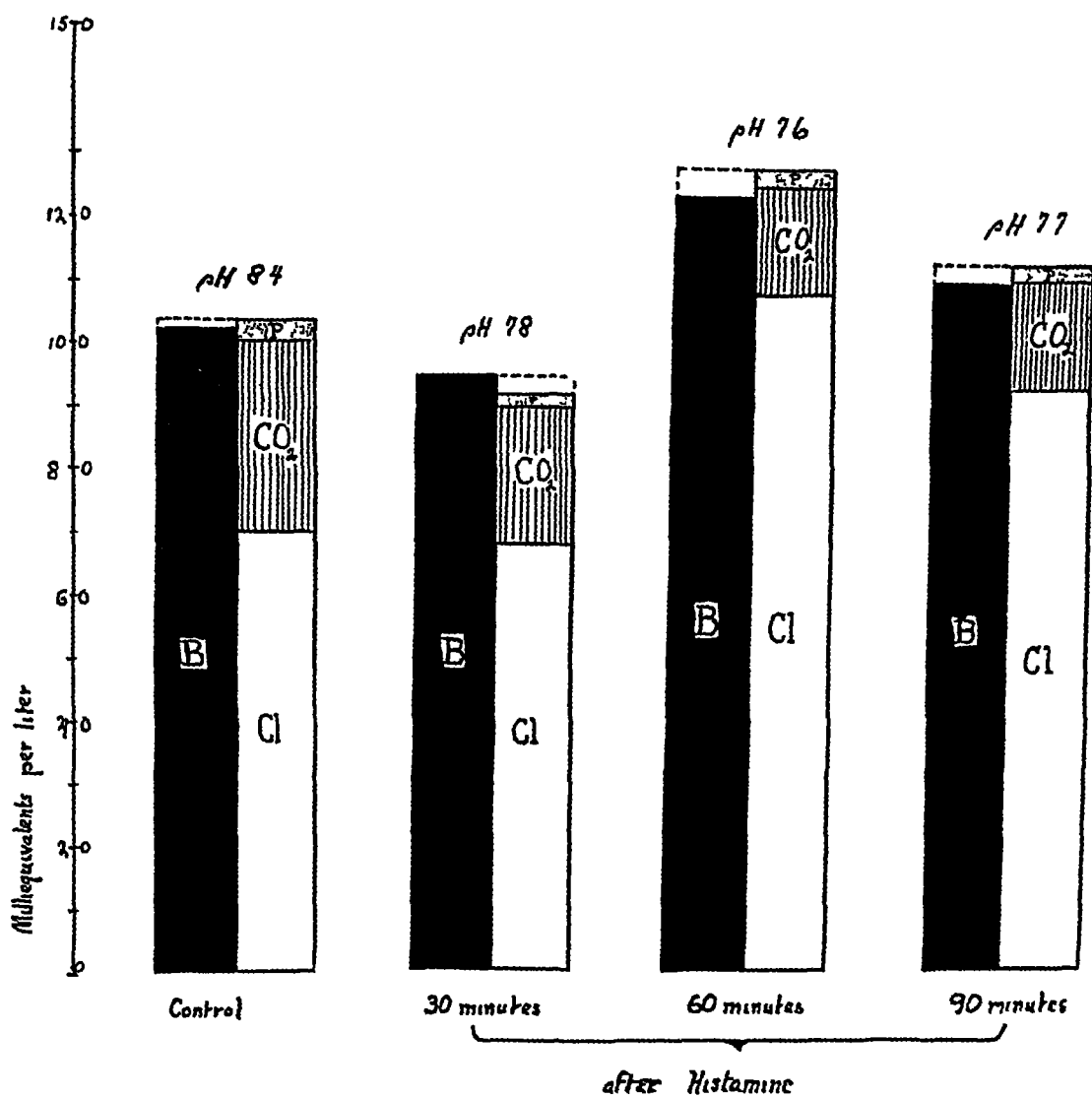


FIG 7 Typical case in Group III (achlorhydria) showing electrolytic changes during histamine stimulation.

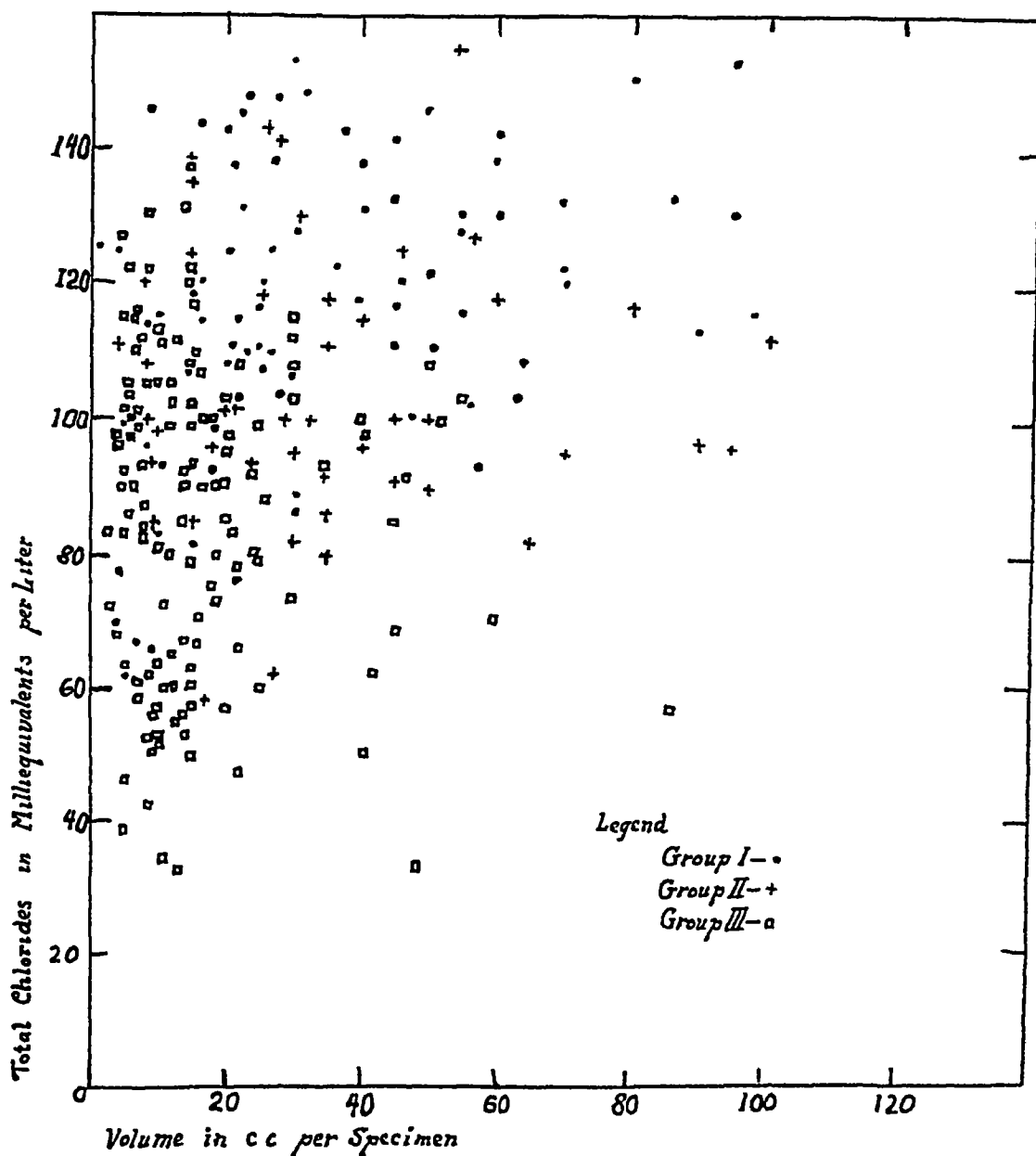


CHART 2 Relation of total chlorides to volume of extracted gastric juice in the several groups

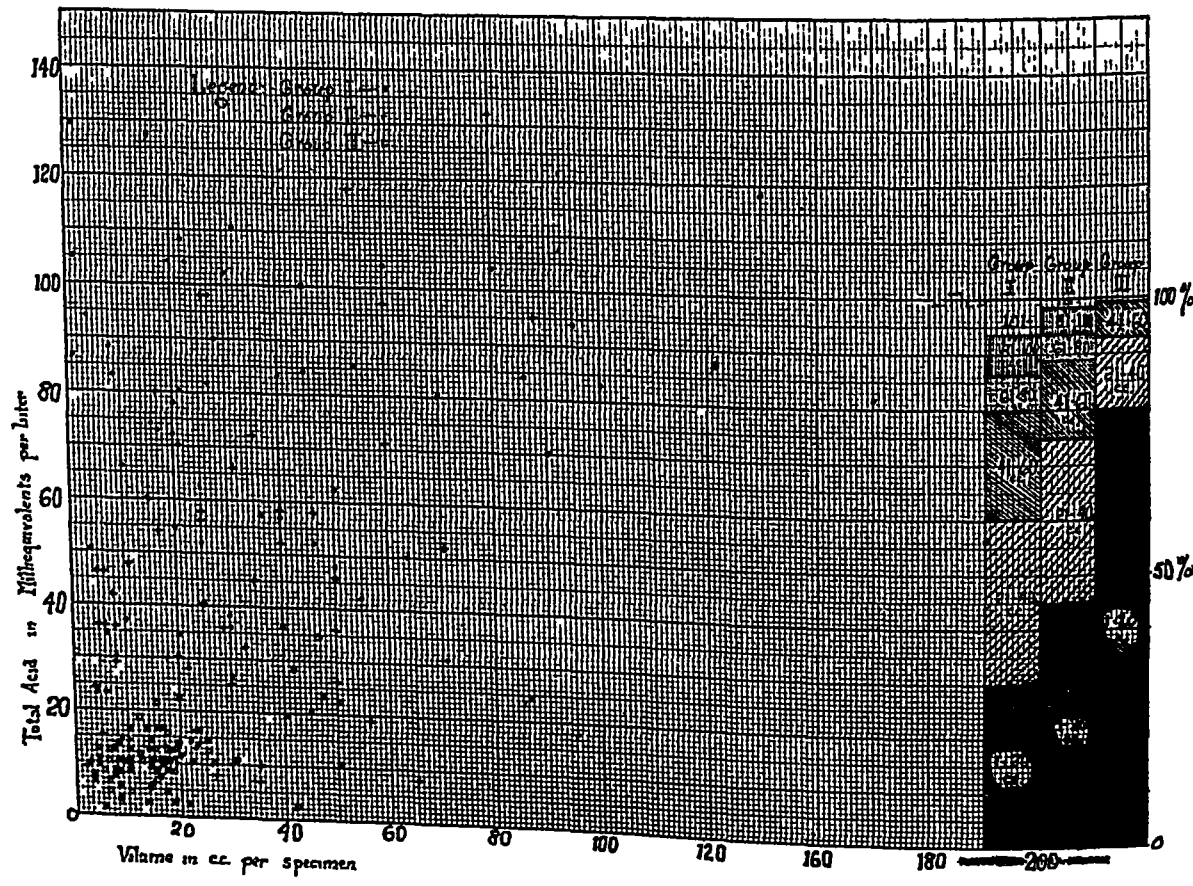


CHART 3 The dots, crosses and squares represent the relation of total acidity to the volume of the extracted specimen of gastric juice in fifty cases. The block figures represent the percentage of specimens for each group arranged according to the volume content. The entire 102 cases were used in the estimation.

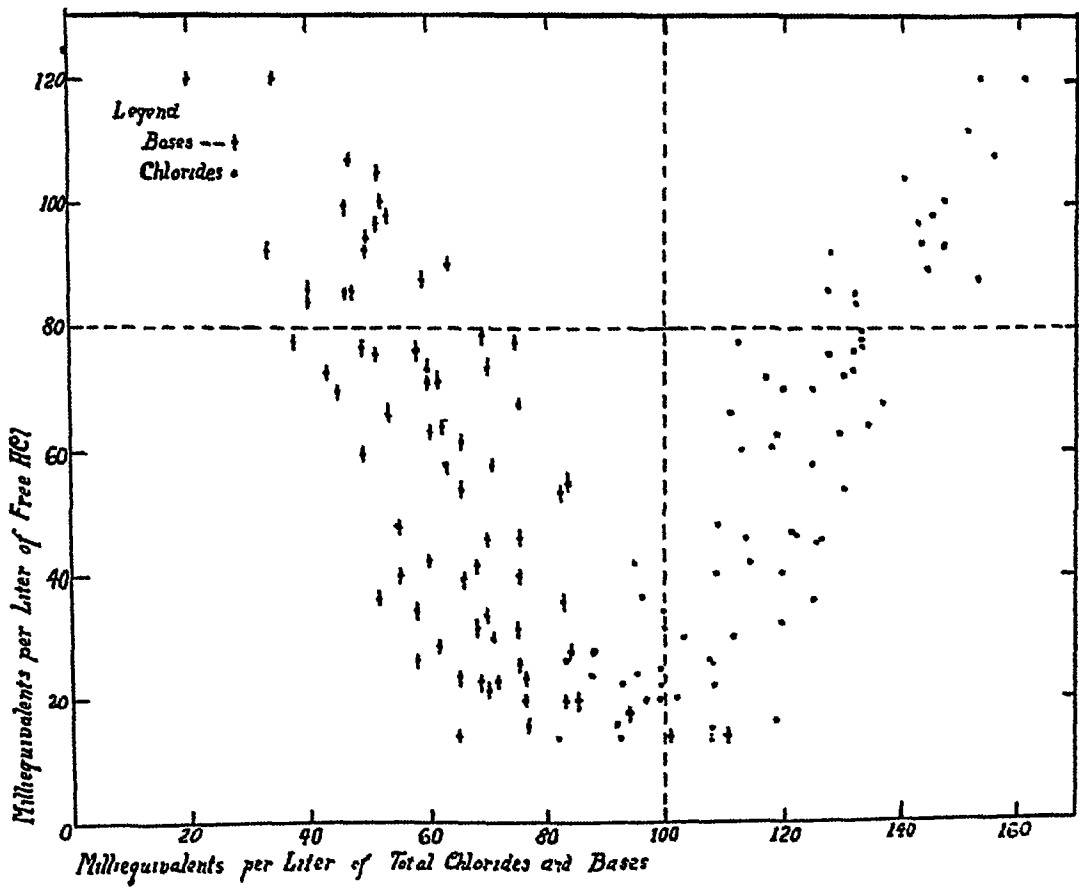


CHART 4 Relation of free hydrochloric acid to bases and total chlorides

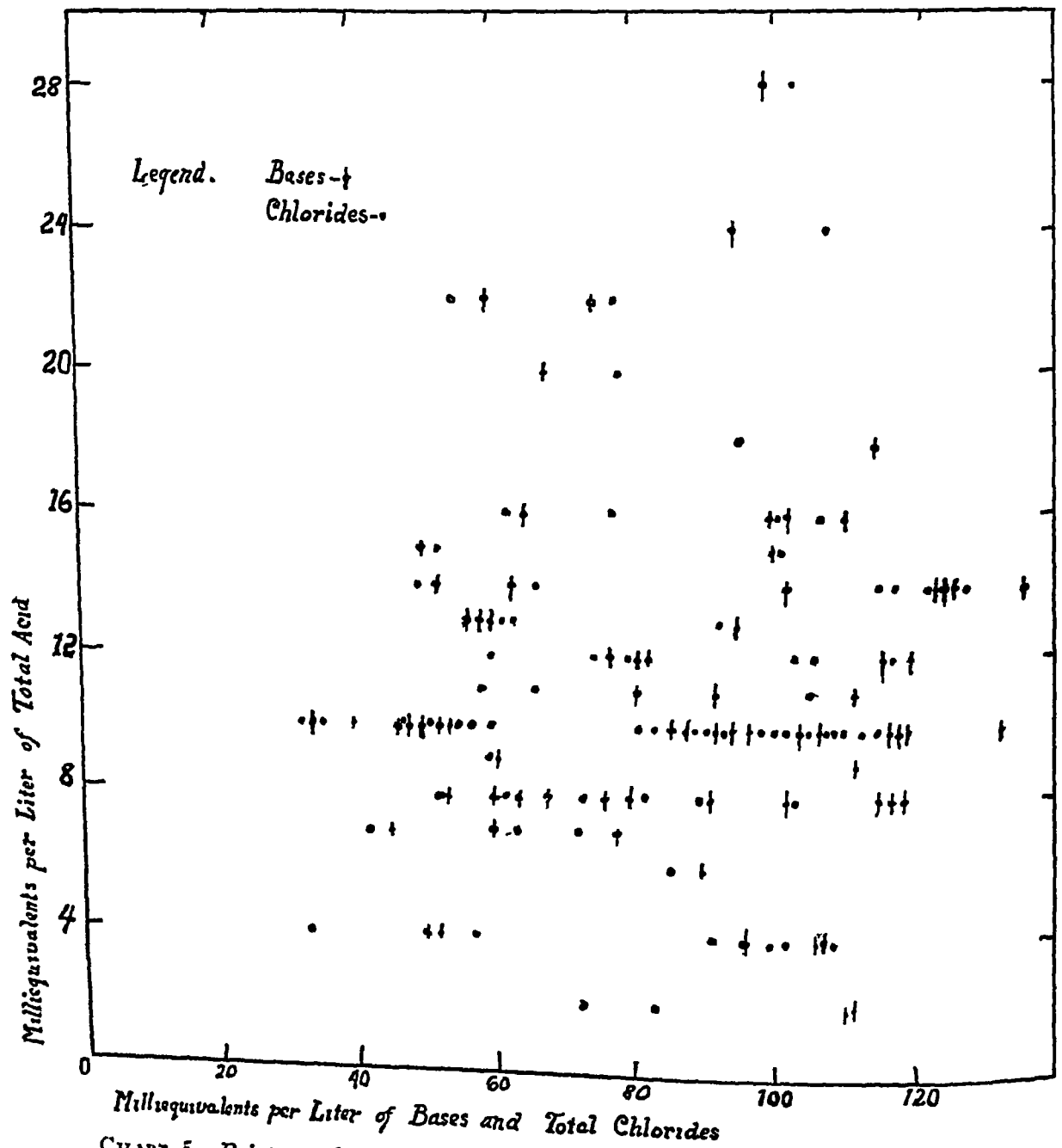


CHART 5 Relation of total acid to bases and total chlorides in specimens with pH 30 to 80

TABLE I
Data on Patients in Group I Who Secrete Free Hydrochloric Acid into
All Specimens of Gastric Juice

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME c c	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ TRYP- Vol- UME %	SIN UNITS
					MILLIEQUIVALENTS	PER LITER					
6	F*	Clear	1.6	15	21	117	94	27			
	30	Clear	1.4	74	77	133	59	24			
	60	Clear	1.2	50	97	145	51	30			
	90	Clear	1.4	22	64	131	62	26			
7	F	Clear	1.8	10	23	93	69	30			
	30	Clear	1.6	64	40	108	66	23			
	60	Clear	1.5	20	66	114	54	23			
8	F	Clear	1.6	10	54	81	26	21			
	30	Bile tr	1.4	80	94	120	30	15			
	60	Clear	1.6	22	20	108	84	11			
8	F	Clear, mucus	1.6	30	24	88	65	27		21	
	30	Clear, mucus	1.4	100	74	120	45	18		21	
	60	Clear, mucus	1.2	95	85	130	40	12		40	
	90	Clear, mucus	1.2	55	86	130	40	15		21	
13	F	Clear		20	20	97	76	32			
	30	Clear		90	60	113	50	32			
	60	Clear		30	92	128	33	26			
	90	Clear		8	78	113	38	27			
31	F	Clear	1.9	190	46	113	70	27			0
	30	Clear	1.2	150	112	151	46	21			20
	60	Clear	1.2	32	100	148	52	19			43
	90	Clear	1.2	27	90	147	62	18			30
38	F	Mucus		4	46	77	36				
	30	Mucus		6	23	67	43				
	60	Mucus		4	12	68	56				
42	F	Clear	2.3	46	42	120	75	27			tr
	30	Clear	1.7	40	73	117	43	26			10
	60	Clear	1.8	45	75	132	58	27			15
43	F	Clear	2.1	20	62	124	65	28		21	0
	30	Clear	1.9	27	74	138	69	23		21	0
	60	Clear	1.3	80	120	150	34	27		21	0
	90	Clear	1.3	16	120	143	20	27		40	0
45	F	Bile tr	2.5		32	118	78	24		30	0
	30	Clear	2.2	170	72	130	60	24		40	0
	60	Clear	2.2	345	72	131	60	24		30	0
	90	Bile tr	2.1	55	76	127	50	24		49	0
54	F	Mucus	1.7	1	78	125	47				tr
	30	Mucus +++	1.5	2	98	140	44				tr
	60	Mucus ++	1.4	2	121	158	40				tr
	90	Mucus	1.5	4	89	125	35				0

*F—Fasting or control specimen

TABLE I (Continued)

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL- UME cc	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ TRYPSIN
					MILLIEQUIVALENTS PER LITER				UMES %	UNITS
65	F	Clear	16	20	94	143	50	31		0
	30	Clear	16	23	93	147	50	31		0
	60	Clear	17	22	98	145	53	28		0
	90	Clear	18	21	68	137	75	27		0
79	F	Clear	24	55	30	103	75	14		0
	30	Clear	17	86	73	132	60	11		0
	60	Bile "B"	20	36	46	122	75	10		0
	90	Bile "A"	23	40	24	96	75	16		0
94	F	Clear	24	8	20	95	73	20	21	0
	30	Clear	19	21	58	102	48	20	20	0
	60	Clear	15	16	62	120	62	10	19	0
	90	Clear	18	9	72	145	70	04	19	0
98	F	Clear	28	45	10	85	75	17	26	20
	30	Clear	16	70	70	121	50	08	17	0
	60	Clear	18	50	52	121	68	05	18	10
	90	Clear	19	30	28	108	82	11	21	0
99	F	Clear	21	25	42	108	50	05	88	tr
	30	Clear	18	60	82	138	48	08	17	tr
	60	Clear	16	60	94	141	48	06	17	tr
	90	Clear	16	45	92	141	54	04	12	tr
101	F	Clear	28	30	12	88	82	10	21	0
	30	Clear	19	50	36	110	84	06	21	0
	60	Clear	18	25	78	118	78	03	30	0
	90	Clear	17	40	50	131	84	03	21	0
104	F	Bile tr	23	18	19	92 ^{Fr}	82	16	49	24
	30	Clear	15	22	76	131	60	08	21	0
	60	Clear	12	130	108	143	42	07	17	0
	90	Bile tr	19	25	50	110	70	10	17	30
113	F	Clear	26	63	8	103	92	14		
	30	Clear	24	47	26	100	76	10		
	60	Clear	23	130	58	111	53	10		
	90	Clear	23	90	48	105	51	10		
114	F	Clear		29	42	103	68			
	30	Clear		5	12	62	50			
	60	Clear		8	15	65	50			
	90	Mucus +++++		13	0	78	78			
114	F	Light green		45	27	99	68	14		
	30	Clear		15	20	81	48	15		
	60	Clear		45	68	112	37	10		
	90	Light yellow		25	43	110	67	19		

TABLE I (Continued)

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME c c	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASIS	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ , TRYPSIN VOL-UMES %	UNITS
					MILLIEQUIVALENTS PER LITER						
115	F	Clear, green	2.6	57	28	93	59				
	30	Clear, green	2.2	28	40	110	71				
	60	Clear, green	1.9	60	76	130	56				
	90	Clear, green	2.0	27	70	125	56				
116	F	Clear		18	36	97	58	1.9			
	90	Clear		98	73	116	39	1.4			
	60	Clear		45	80	116	37	1.4			
	90	Clear		55	73	116	39	1.4			
117	F	Bile tr	2.4	10	40	115	68	2.4			0
	30	Bile tr	2.6	15	30	107	75	2.0			0
	60	Bile tr	2.6	21	34	111	67	2.0			0
	90	Bile tr	2.4	12	36	113	69	2.2			0
118	F	Clear	1.6	40	86	138	50	1.9			
	30	Clear	1.4	38	100	142	44	1.5			
	60	Clear	1.4	30	116	152	39	1.7			
	90	Clear	1.3	95	118	153	35	1.7			

TABLE II

Data on Patients in Group II Who Secrete no Free Hydrochloric Acid into the Fasting Specimen of Gastric Juice But Who Do Secrete It After Stimulation By Histamine

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME c c	Free HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ TRYPSIN
					MILLIEQUIVALENTS	PER LITER		UMES %		UNITS
10	F*	Clear, mucus	4.0	95	2	96	90	1.6		tr
	30	Clear	2.2	60	61	118	51	0.8		0
	60	Clear	2.2	35	62	118	52	0.7		0
	90	Bile "A"	6.8	20	0	102	103	0.7		4.2
11	F		3.7	10	6	111	99	1.7		
	30		2.3	25	50	109	55	2.1		
	60		2.4	18	37	96	53	2.4		
12	F	Clear, mucus	7.0	35	0	92	97	1.7		0
	30	Clear	2.4	50	32	100	68	4.2		0
	60	Clear	2.2	40	42	100	56	4.7		0
17	F			0						
	30	Mucus +++++		35	30	111	71	3.6		
	60	Mucus +++++		5	34	100	58	3.0		
15	F	Clear	3.8	56	4	93	81	1.6		
	30	Clear	2.6	45	12	91	77	1.8		
	60	Clear	2.5	45	24	100	71	0.9		
16	F	Clear	4.0	40	6	96	89	2.3		3.0
	30	Clear	2.0	50	30	90	56	0.7		2.0
	60	Clear	1.8	35	42	86	44	1.5		3.0
	90	Clear, mucus	5.0	35	4	80	89	1.7		2.5
26	F	Clear, green	6.8	65	0	82	91	2.4		13.3
	30	Clear, green	1.8	70	42	95	60	1.6		15.4
	60	Tr "B" bile	3.1	30	14	82	65	2.3		16.0
40	F	Clear	7.1	18	0	80	82	2.1		0
	30	Clear	2.4	29	24	100	75	2.1	5.9	2.0
	60	Tr "B" bile	2.4	20	22	102	71	2.0	2.1	3.7
	90	Tr "B" bile	2.5	33	20	100	84	1.6	3.0	3.0
44	F	Clear	6.8	30	0	95	95	3.0		2.0
	30	Clear	7.3	35	0	74	78	2.5	4.7	2.0
	60	Clear	2.1	40	50	115	67	2.4	6.6	3.3
50	F	Bile "A"	7.8	9	0	85	90	5.4		11.2
	30	Clear	2.4	6	38	98	60	3.9		4.0
	60	Bile "A"	2.4	6	28	100	74	3.9		4.1
	90	Bile "A"	7.4	6	17	90	69	4.7		8.2
52	F	Mucus	6.8	2	0					6.0
	30	Mucus	2.8	8	22	120	98			4.0
	60	Mucus		4	16	111	95			5.0

*F—Fasting or control specimen

TABLE II (Continued)

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME cc	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ TRYPSIN	
					MILLIEQUIVALENTS PER LITER					VOL-UMES %	UNITS
61	F	Mucus +++	7.9	15	0	85	90	23		35	
	30	Mucus +++	2.3	5	30			22		20	
	60	Mucus +++	3.4	5	8			23		20	
	90	Mucus +++	7.9	15	0	73	76	22		35	
73	F	Clear	6.8	27	0	62	68	19		0	
	30	Clear	1.5	88	86	127	46	20		0	
	60	Clear	1.4	54	108	155	46	12		0	
	90	Clear	1.8	26	88	143	58	14		0	
78	F	Clear, mucus	7.9	17	0	58	60	23	90	202	0
	30	Clear	1.7	31	54	130	65	17		21	0
	60	Clear	1.6	17	70	125	58	15		20	0
	90	Clear	1.9	17	42	114	68	17		21	0
87	F	Blood	7.1	19	0	107	101	16			56
	30	Mucus ++++	2.4	18	18	110	90	13			20
	60	Mucus	2.2		38	129	90	0.8			0
	90	Blood, mucus	2.3	8	32						
89	F	Clear, mucus	6.7	8	0	93	96	11			
	30	Clear	2.4	25	30	105	80	11			
	60	Clear	2.0	25	44	118	80	18			
	90	Clear	2.6	8	25	108	80	12			
95	F	Clear, mucus	6.9	10	0	98	110	2.9	107	238	52
	30	Clear	2.4	4				0.8		17	0
	60	Clear	2.2	15	42	123	80	0.5		40	0
	90	Clear	2.2	15	30	135	103	0.5		21	0
102	F	Clear	7.0	24	0	93	109	3.0	110	246	tr
	30	Clear	2.1	46	48	125	85	1.6		10	0
	60	Clear	1.7	28	78	141	70	1.2		10	0
	90	Clear	1.9	15	50	137	84	1.2		10	0
105	F			0							
	30	Clear	2.0	170	38	95	60	1.3		21	0
	60	Clear	1.8	100	52	112	62	1.0		21	0
	90	Clear	1.6	80	60	117	60	1.0		21	0
119	F	Mucus ++++	6.8	18	0	80	88				
	30	Mucus +	1.9	45	50	113	55				
	60	Mucus +	1.6	57	80	127	49				
	90	Mucus, Blood	1.9	90	48	96	43				
120	F	Clear	7.6		0	96	93				
	30	Clear	3.0		16	86	59				
	60	Clear	2.5		25	88	57				
	90	Clear	4.5		2	80	67				

TABLE III
Data on Patients in Group III Who Secrete no Free Hydrochloric Acid into the Gastric Juice Either Before or After Stimulation

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME c c	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ VOL-UMES %	TRYP-SIN UNITS
					MILLIEQUIVALENTS PER LITER						
14	F*	Yellow	7.6	25	0	79	91	3.3			
	30	Mucus	7.8	20	0	85	103	3.2			
	60	Yellow, mucus	7.6	8	0						
19.	F	Bile tr	6.8	42	0	62	65	2.2			
	30	Clear	6.8	24	0	80	75	2.9			
	90	Bile tr	6.8	25	0	60	64	3.7			
21	F	Yellow	7.4	55	0	103	117	1.6	85	189	
	60	Clear, mucus	6.8	5	0	127	123	1.2			
21	F	Pale yellow	7.0	50	0	108	116	4.0			
	30	Pale yellow	6.8	6	0	98	101	3.3			
	60			0							
21	90	Pale yellow	6.6	26	0	88	86	2.8			
23	F		7.3	8	0	83	102	3.1			
	30		7.2	8	0	83	96	3.3			
	60		6.7	15	0	93	95	3.4			
	90		7.3	5	0	90	102	4.5			
24	F		6.8	8	0	95	115	5.3			138
	30		6.2	3	0			4.0			
	60			0							
24	90		5.2	7	0	75	79	3.3			82
25	F		7.4	10	0	57	50	5.3			109
	30		6.8	14	0	53	54	5.3			150
	60		3.6	12	4	65	65	6.0			41
	90		6.9	3	0						
28	F	Bile "A"	7.0	30	0	103	116	5.3			58
	30	Tr bile	7.6	5	0	92	100	4.3			78
	60	Tr bile	7.2	15	0	102	103	4.3			84
	90	Bile "A"	7.0	38	0			4.4			78
29	F		7.8	30	0	115	135	3.0			0
	30		7.6	20	0	113	132	1.5			20
	60			0							
29	90		7.6	15	0	117		1.9			40
30	F		7.3	5	0	101	110	4.0			55
	30			2	0						80
30	(A)		6.5	15	0	123	123	5.4			90
33	F		7.0	7	0	100	115	3.7			57
	30		7.4	7	0	115	116	3.0			20
	(A)		7.0	5	0	115	113	2.7			83

*F = first of control specimen

TABLE III (Continued)

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME c c	Free HCl	Total Chlorides as Chloride Ion	Base	P as Phosphate Ion	CO ₂ as HCO ₃ Ion	CO ₂ Vol-UMES %	TRYPT-SIN UNITS
					MILLIEQUIVALENTS PER LITER						
35	F			1							
	30		66	86	0	57	67	49			63
	60		67	40	0	50	48	48			80
35 (90)	F	Mucus, bile	71	16	0	66	92	20	130	290	130
	30	Mucus	72	12	0	60	81	32	117	260	90
	60	Mucus	72	48	0	33	50	32	80	170	70
	90	Tr bile	69	18	0	78	100	31	90	200	180
39	F			15	0	50	55				93
	30			5	0	38	42				80
	60			5	0	46	50				95
51	F	Bile +	75	6	0	100	114	55	54	120	0
	30	Bile +	73	6	0	105	119	40	58	126	40
	60	Bile tr	71	9	0	122	132	28	58	126	56
55	F		79	10	0	52	54				57
	30		78	10	0	35	34				31
	90		80	8	0	42	45				35
56	F	Mucus +++++	71	8	0	87	94				40
	30	Mucus +++++	67	3	0	83	89				40
	60	Mucus +++++	67	3	0	72	78				40
	90	Mucus +++++	72	5	0	83	88				56
57	F	Mucus +++++		4	0	97	100				21
	30	Mucus +++++		4	0	97	99				56
	60	Mucus +++++		7	0	110	112				103
	90	Mucus +++++		15	0	79	80				106
58	F	Bile +	70	10	0	53	50				112
	30	Bile +	69	10	0	63	65				135
	60	Bile +	72	5	0	63	59				116
	90	Bile +	67	10	0	81	81				116
58	F	Clear	84	13	0	33	40	11			35
	30	Bile +	72	20	0	57	60	16			185
	60	Bile +	72	22	0	78	75	21			165
	90	Clear	79	16	0	107	109	18			146
59	F	Clear	70	14	0	56	57				120
	30	Bile +	70	7	0	58	60				90
	60	Bile +	70	6	0	86	88				
	90	Bile +	70	6	0	103	102				98
60	F		73	15	0	63	69	34			
	30		67	7	0	61	58	34			
	60		62	15	0	69	61	34			

TABLE III (Continued)

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UMI c c	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ TRYPSIN VOL-UMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS	PER LITER		PER LITER	PER LITER	PER LITER	PER LITER
64	30		3.5	22	8	66	63	5.6			
	60			22	0	47	50	5.2			
68	F		7.9	19	0	90	98	3.4			5.6
	30		7.9	8	0	93	103	2.6			7.6
	90			4	0			3.4			11.2
70	F	Clear	7.9	14	0	92	99	4.4			tr
	30	Clear	7.9	19	0	73	116	4.1			tr
	60	Bile +	7.9	21	0	83	110	4.1			tr
	90	Bile +++	7.8	14	0	90	105	4.4			12.3
77	F	Light bile +	7.9	18	0	75	77	3.6			.
	30	Light bile +	6.9	41	0	98	99	4.1			
	60	Light bile +	7.1	47	0	91	94	3.1			
	90	Bile +++	7.8	19	0	90	91	2.9			
83	F	Mucus ++++	7.2	17	0	90	92	2.4			
	30	Mucus ++++	7.2	24	0	92	94	2.4			
	60	Light bile	6.9	20	0	95	95	1.3			
	90	Mucus ++++	6.7	15	0	99	102				
86	F	Mucus	8.4	3	0						
	30	"B" bile	7.0	7	0	116	119	1.9			16.9
	60	Blood, mucus	7.3	9	0	130	132	2.7			
88	F	Bile tr	7.1	16	0	110	121	2.2	11.6	25.8	9.0
	30	Bile tr	7.1	10	0	105	114	2.2	9.9	21.7	8.0
	60	Bile tr	7.9	12	0	105	117	2.1	12.5	27.7	11.0
	90	Bile tr	7.9	18	0	100	117	1.6	12.5	27.7	13.0
97	F	Bile tr	7.0	10	0	50	65	2.8	12.3	27.0	
	30	Bile +	7.0	15	0	57	66	2.8	10.7	24.0	
	60	Bile +	6.7	12	0	60	62	3.1	6.7	15.0	
	90	Clear	6.7	13	0	55	59	2.6	5.8	13.0	
107	F	Clear	7.2	10	0	113	120	2.9	7.0	15.5	
	60	Bile tr	3.7	14	12	131	125	0.7	8.7	19.2	
	90	Bile tr	7.2	11	0	111	120	1.5	5.7	12.6	
108	F	Bile +	8.3	52	0	100	109	2.7	24.6	52.2	
	60	Bile +	8.5	22	0	108	118	1.4	23.0	50.4	
109	F	Bile tr	6.8	20	0	103	112	0.9		2.1	
	30	Bile tr	5.8	20	9	113	114	0.8		2.1	
	60	Bile tr	5.9	15	11	120	124	0.9		1.0	
	90	Bile tr	6.8	30	0	112	130	1.4		1.1	
110	F	Clear, mucus	6.7	15	0	108	113	1.9	5.7	12.6	
	60	Clear, mucus	7.1	15	0	137	140	1.4	4.7	10.7	

TABLE III (Continued)

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME c c	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASIC	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ TRYPTOPHAN VOL-UMES %	TRYPTOPHAN UNITS
					MILLIEQUIVALENTS PER LITER						
111	F	Bile tr	24	12	0	102	118	25	83	183	
	30	Bile tr	77	6	0	97	103	19	65	145	
	90	Bile tr		18	0	100	46 ²	20	48	107	
112	F	Clear	84	60	0	70	112	31	300	673	
	30	Clear	78	45	0	68	95	19	219	485	
	60	Clear	76	30	0	108	112	27	170	381	
	90	Clear	77	35	0	93	106	22	175	390	
121	F	Clear	69	3	0						
	30	Clear	59	4	0	68	72				
	60	Clear	68	10	0	56	65				
	90	Clear	68	10	0	43	61				
122	F	Mucus	65		0	58	95				
	30	Mucus	71		0	60	90				
	60	Mucus	69		0	67	95				
	90	Mucus	63		0	86	89				
123	F	Clear	77	16	0	70	87	21			0
	30	Bile tr	74	10	0	90	96	28			0
	60	Clear	67	6	0	122	123	21			0
	90	Bile +	67	8	0	112	120	33			0
124	F	Mucus +++	74	11	0	72	94	41	190	427	
	30	Mucus +	76	12	0	80	97	43	143	316	
	60	Mucus +	77	14	0	67	82	43	103	230	
	90	Mucus ++++	77	9	0	62	85	43	106	236	
125	F	Clear, mucus	74		0	64	93				0
	30	Clear, mucus	70		0	55	60				0
	60	Clear, mucus	72		0	70	80				0
	90	Mucus, bile	74		0	73	95				0
126	F	Clear		30	0	73	83	42			0
	30	Clear		40	0	75	80	50			0
	60	Clear	..	6	0	90	98	50			68
	90	Clear		13	0	112	128	46			tr
127.	F	Clear	76	12	0	99	112	30	95	210	.
	30	Clear	71	14	0	85	94	27	64	140	
	60	Bile tr	68	25	0	99	103	34	54	122	
	90	Bile tr	74	8	0	105	115	39	44	99	

TABLE III (Continued)

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME c c	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO ₂ AS HCO ₃ ION	CO ₂ VOL-UMES %	TRYP-SIN UNITS
					MILLIEQUIVALENTS PER LITER						
64	30		3.5	22	8	66	63	5.6			
	60			22	0	47	50	5.2			
68	F		7.9	19	0	90	98	3.4			5.6
	30		7.9	8	0	93	103	2.6			7.6
	90			4	0			3.4			11.2
70	F	Clear	7.9	14	0	92	99	4.4			tr
	30	Clear	7.9	19	0	73	116	4.1			tr
	60	Bile +	7.9	21	0	83	110	4.1			tr
	90	Bile +++	7.8	14	0	90	105	4.4			12.3
77	F	Light bile +	7.9	18	0	75	77	3.6			
	30	Light bile +	6.9	41	0	98	99	4.1			
	60	Light bile +	7.1	47	0	91	94	3.1			
	90	Bile +++	7.8	19	0	90	91	2.9			
83	F	Mucus ++++	7.2	17	0	90	92	2.4			
	30	Mucus ++++	7.2	24	0	92	94	2.4			
	60	Light bile	6.9	20	0	95	95	1.3			
	90	Mucus ++++	6.7	15	0	99	102				
86	F	Mucus	8.4	3	0						16.9
	30	"B" bile	7.0	7	0	116	119	1.9			
	60	Blood, mucus	7.3	9	0	130	132	2.7			
88	F	Bile tr	7.1	16	0	110	121	2.2	11.6	25.8	9.0
	30	Bile tr	7.1	10	0	105	114	2.2	9.9	21.7	8.0
	60	Bile tr	7.9	12	0	105	117	2.1	12.5	27.7	11.0
	90	Bile tr	7.9	18	0	100	117	1.6	12.5	27.7	13.0
97	F	Bile tr	7.0	10	0	50	65	2.8	12.3	27.0	
	30	Bile +	7.0	15	0	57	66	2.8	10.7	24.0	
	60	Bile +	6.7	12	0	60	62	3.1	6.7	15.0	
	90	Clear	6.7	13	0	55	59	2.6	5.8	13.0	
107	F	Clear	7.2	10	0	113	120	2.9	7.0	15.5	
	60	Bile tr	3.7	14	12	131	125	0.7	8.7	19.2	
	90	Bile tr	7.2	11	0	111	120	1.5	5.7	12.6	
108	F	Bile +	8.3	52	0	100	109	2.7	24.6	52.2	
	60	Bile +	8.5	22	0	108	118	1.4	23.0	50.4	
109	F	Bile tr	6.8	20	0	103	112	0.9		2.1	
	30	Bile tr	5.8	20	9	113	114	0.8		2.1	
	60	Bile tr	5.9	15	11	120	124	0.9		1.0	
	90	Bile tr	6.8	30	0	112	130	1.4		1.1	
110	F	Clear, mucus	6.7	15	0	108	113	1.9	5.7	12.6	
	60	Clear, mucus	7.1	15	0	137	140	1.4	4.7	10.7	

TABLE III (Continued)

CASE NO	TIME MIN-UTES	DESCRIPTION	pH	VOL-UME c c	Free HCl	Total Chloride's as Chloride Ion	BASIS	P AS PHOSPHATE Ion	CO ₂ AS HCO ₃ Ion	CO ₂ VOL-UMES %	TRYP-SIN UNITS
					MILLIEQUIVALENTS PER LITER						
111	F	Bile tr	2.4	12	0	102	118	2.5	8.3	18.3	
	30	Bile tr	7.7	6	0	97	103	1.9	6.5	14.5	
	90	Bile tr		18	0	100	46 ^p	2.0	4.8	10.7	
112	F	Clear	8.4	60	0	70	112	3.1	30.0	67.3	
	30	Clear	7.8	45	0	68	95	1.9	21.9	48.5	
	60	Clear	7.6	30	0	108	112	2.7	17.0	38.1	
	90	Clear	7.7	35	0	93	106	2.2	17.5	39.0	
121	F	Clear	6.9	3	0						
	30	Clear	5.9	4	0	68	72				
	60	Clear	6.8	10	0	56	65				
	90	Clear	6.8	10	0	43	61				
122	F	Mucus	6.5		0	58	95				
	30	Mucus	7.1		0	60	90				
	60	Mucus	6.9		0	67	95				
	90	Mucus	6.3		0	86	89				
123	F	Clear	7.7	16	0	70	87	2.1			0
	30	Bile tr	7.4	10	0	90	96	2.8			0
	60	Clear	6.7	6	0	122	123	2.1			0
	90	Bile +	6.7	8	0	112	120	3.3			0
124	F	Mucus +++	7.4	11	0	72	94	4.1	19.0	42.7	
	30	Mucus +	7.6	12	0	80	97	4.3	14.3	31.6	
	60	Mucus +	7.7	14	0	67	82	4.3	10.3	23.0	
	90	Mucus +++++	7.7	9	0	62	85	4.3	10.6	23.6	
125	F	Clear, mucus	7.4		0	64	93				0
	30	Clear, mucus	7.0		0	55	60				0
	60	Clear, mucus	7.2		0	70	80				0
	90	Mucus, bile	7.4		0	73	95				0
126	F	Clear		30	0	73	83	4.2			0
	30	Clear		40	0	75	80	5.0			0
	60	Clear		6	0	90	98	5.0			68
	90	Clear		13	0	112	128	4.6			tr
127	F	Clear	7.6	12	0	99	112	3.0	9.5	21.0	
	30	Clear	7.1	14	0	85	94	2.7	6.4	14.0	
	60	Bile tr	6.8	25	0	99	103	3.4	5.4	12.2	
	90	Bile tr	7.4	8	0	105	115	3.0	4.4	9.0	

TABLE IV

Computation of the percentage of HCl and NaCl in extracted specimens
 From this is figured the strength at which these chemicals have originated in pure solution and the amount of that solution in c c The calculation is given on page 18

CASE No	TIME MIN-UTES	VOLUME c c	MILLIEQUIVALENTS			SPECIMEN PERCENTAGE		VOLUME IN c c		SECRETION CONCENTRATION	
			HCl	Cl-	BASE	HCl	NaCl	HCl	NaCl	HCl	NaCl
8	F	30	24	88	65	086	377	8 1	21 9	320	515
	30	100	74	120	45	266	261	62 2	37 8	428	690
	60	95	85	136	40	306	232	64 6	30 4	450	725
	90	55	86	130	40	309	232	37 5	17 5	453	730
10	F	90	2	96	90	0	522	0	90 0	0	522
	30	60	61	118	51	220	296	32 1	27 9	407	650
	60	35	62	118	52	228	302	19 0	16 0	407	650
	90	20	0	102	105	0	608	0	20 0	0	608
23	F	8	0	83	102	0	592	0	8 0	0	592
	30	8	0	83	96	0	556	0	8 0	0	556
	60	15	0	93	95	0	551	0	15 0	0	551
	90	5	0	90	102	0	592	0	5 0	0	592
31	F	190	46	113	70	166	406	75 3	114 7	417	673
	30	150	112	151	46	403	267	106 3	43 7	567	916
	60	32	100	148	52	360	302	21 0	11 0	547	881
	90	27	90	147	62	324	359	16 0	11 0	547	881
40	F	18	80	80	82	0	475	0	18 0	0	475
	30	29	24	100	75	086	434	7 4	21 6	360	580
	60	20	22	102	71	079	415	4 4	15 6	367	590
	90	33	20	100	84	070	487	16 6	16 4	360	580
44	F	30	0	95	95	0	552	0	30 0	0	552
	30	35	0	74	78	0	454	0	35 0	0	454
	60	40	50	115	67	180	388	17 1	22 9	422	667
56	F	8	0	87	94	0	545	0	8 0	0	545
	30	3	0	83	89	0	515	0	3 0	0	515
	60	3	0	72	78	0	453	0	3 0	0	453
	90	5	0	83	88	0	510	0	5 0	0	510
58	F	13	0	33	40	0	232	0	13 0	0	232
	30	20	0	57	60	0	348	0	20 0	0	435
	60	22	0	78	75	0	435	0	22 0	0	435
	90	16	0	107	109	0	632	0	16 0	0	632
73	F	27	0	62	68	0	395	0	27 0	0	395
	30	88	86	127	46	309	267	57 3	30 7	476	765
	60	54	108	155	46	288	267	37 9	16 1	526	894
	90	20	88	143	58	313	336	14 7	10 7	555	846
78	F	17	0	58	60	0	348	0	17 0	0	348
	30	31	54	130	65	194	376	14 0	17 0	429	690
	60	17	70	125	58	257	334	9 3	7 7	461	742
	90	17	42	114	68	151	394	6 5	10 5	396	638
79	F	55	30	103	75	108	435	15 7	39 3	378	609
	30	85	73	132	60	263	348	47 2	38 3	479	772
	60	26	46	122	75	166	435	12 9	21 1	436	707
	90	20	24	96	75	086	435	9 7	30 3	356	575
82	F	45	10	83	75	036	435	5 3	39 7	306	493
	30	70	70	121	50	252	290	40 8	29 2	432	696
	60	50	52	121	68	187	394	21 7	28 3	432	696
	90	21	25	103	82	101	475	7 6	22 4	396	637

TABLE IV (Continued)

CASE No	TIME MIN-UTES	VOL-UME c c	MILLIEQUIVALENTS			SPECIMEN PERCENTAGE		VOLUME IN c c		SECRETION CONCENTRATION	
			HCl	Cl-	BASE	HCl	NaCl	HCl	NaCl	HCl	NaCl
102	F	24	0	93	109	0	540	0	24 0	0	540
	30	46	48	125	85	177	494	16 6	29 4	479	761
	60	28	78	141	70	280	406	14 8	13 2	533	858
	90	15	50	137	84	180	488	5 6	9 4	483	767
113	F	63	8	103	92	029	530	5 0	58 0	370	598
	30	47	26	100	76	093	441	12 0	35 0	360	580
	60	130	58	111	53	290	307	67 8	62 2	400	643
	90	90	48	105	51	173	295	43 2	46 8	379	609

TABLE V

Data to Demonstrate that NaCl Is not Secreted at a Constant Level

CASE No	TIME MIN-UTES	VOL-UME c c	HCl meq	Cl- meq	BASE meq	As found	SPECIMEN PERCENTAGE OF NaCl	
							If secretion strength had remained at pre-stimulated level and had been secreted in pure solution	Secretion concentration according to formula for NaCl
102	F	24	0	93	109	540	540	540
	30	46	48	125	85	494	345	761
	60	28	78	141	70	406	281	858
	90	15	50	137	84	488	339	767
73	F	27	0	62	68	395	395	395
	30	88	86	127	46	267	138	765
	60	54	108	155	46	267	117	894
	90	26	88	143	58	336	156	846

REFERENCES

- ¹GAMBLE, J L, and McIVER, M A Fixed base in gastric juice, *Proc Soc Exper Biol and Med*, 1925-26, **xxiii**, 439
- ²MACLEAN, H, and GRIFFITHS W J The automatic regulation of gastric acidity, *Jr Physiol*, 1928, **lxxi**, 356
- ³MACLEAN, H, GRIFFITHS, W J, and HUGHES, T A The relationship of peptic activity to neutral chloride secretion during gastric digestion in man, *Jr Physiol*, 1929, **lxxii**, 409
- ⁴BOLDYREFF, W The self-regulation of the acidity of the gastric contents and the real acidity of the gastric juice, *Quart Jr Exper Physiol* 1915, **viii**, 1
- ⁵MACLEAN, H, and GRIFFITHS, W J The factors influencing the concentration of hydrochloric acid during gastric digestion, *Jr Physiol*, 1928, **lxxi**, 63
- ⁶BUIGER, H A, STROUD, C M, and HIRSHMAN, M L Studies of the chemical mechanism of hydrochloric acid secretion I Electrolyte variations in human gastric juice, *Jr Clin Invest*, 1927-28, **v**, 547
- ⁷POLLARD W S, ROBERTS, A M, and BLOOMFIELD, A L The chloride, base and nitrogen content of gastric juice after histamine stimulation, *Jr Clin Invest*, 1927-28, **v**, 611.
- ⁸BLOOMFIELD, A L, ROBERTS, A M, and POLLARD, W S The composition of

- the gastric secretion in cases of anacidity, Trans Assoc Am Phys, 1928, xliii, 242
- ⁹CLARK, W M The determination of hydrogen ions, Third Edition, 1928, Williams and Wilkins, Baltimore
- ¹⁰VAN SLYKE, D D The determination of chlorides in blood and tissues Jr Biol Chem, 1923, lviii, 523
- ¹¹STADIE, W C, and ROSS, E C A micro-method for the determination of base in blood and serum and other biological materials, Jr Biol Chem, 1925, lxxv, 735
- ¹²BENEDICT, S R, and THEIS, R C A modification of the molybdic method for the determination of inorganic phosphorus in serum Jr Biol Chem, 1924, lxi, 63
- ¹³VAN SLYKE, D D, and CULLEN, G E Studies of acidosis I The concentration of the blood plasma, its significance and its determination as a measure of acidosis, Jr Biol Chem, 1927, xxx, 289
- ¹⁴MARTIN, L Biliary, pancreatic and duodenal studies II Estimation of pancreatic enzymes and value of such determinations from a clinical standpoint, Arch Int Med, 1927, xxxix, 343-355
- ¹⁵MICHAELIS, L Some problems concerning the gastric juice, Harvey Lectures, 1926-27, xxi, 59
- ¹⁶VAN SLYKE, D D, HASTINGS, A B, HILLER, A, and SENDROY, J, JR Studies of gas and electrolyte equilibria in blood XIV The amounts of alkali bound by serum albumin and globulin, Jr Biol Chem, 1928, lxxix, 769

The First Aphorism of Hippocrates*

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WE all claim descent, as physicians, from the philosophers and physicians of the great period of Greek civilization, the fifth century, B C , and yet in the rapid increase of current literature we may easily forget what that means. Of course, we can easily revive our knowledge in any of a number of excellent works on Medical History, old or new, or, we can reread any chapter or number of chapters in the Hippocratic Writings. In the following I have chosen one book, namely, the Aphorisms, and traced it down through the centuries, at long intervals, to be sure, seeing how it was reflected by the mind of the most brilliant Greek physician of Pergamos and Rome in the second century, A D ; by some outstanding Arabs of the ninth, tenth and eleventh centuries, a keen and practical Englishman of the fourteenth century, and then through the busy days of early book-printing down to our own time. Ancient and modern critics agree that a great deal, at least, of the Book of Aphorisms is the work of Hippocrates himself, although admitting that additions and alterations have been made. The earliest commentator we know, Galen, believed Hippocrates

produced the Aphorisms in his old age, and as one of the latest commentators, Francis Adams, has said, no one could have written them but one who had long been familiar with the phenomena of disease, and had maturely reflected on all the various subjects to which the Aphorisms relate. That the work was highly valued in the centuries immediately following the lifetime of the author we can gather from the fact that it was taken up by the School of Alexandria, where it was codified and preserved, and in time reached Galen, who, with characteristic enthusiasm and energy arranged the Book of Aphorisms in seven sections, added his own Commentaries and so enabled it to come down through the Dark Ages and not only survive the downfall of Galenism but be used as a text-book up to the time of the discoveries of Percussion and Auscultation, and of the Cell. The characters of the two men, Hippocrates and Galen, have been vividly analyzed recently by Charles Greene Cumston*.

The next name that comes down to us with that of Hippocrates is Hunan, or Honem ben Ishak, a Nestorian Christian better known as Joannitus, born about 809 A D . in a village in Mesopotamia, and the most learned among the translators from Greek into

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Arabic Joannitius was the author of one of the most celebrated "Isagoges", or Introductions to Medicine. Used in the Middle Ages as textbooks in manuscript, these were highly regarded and were therefore among the earliest medical books to be reproduced by printing. I have been fortunate enough to examine a very good example in the library of Dr LeRoy Crummer. Spelling, capitals and abbreviations show the influence of manuscript methods. The title is "Ysagoge Johannis / Incipiunt Ysagoge Joannis / adtegni galien". The place of publication was probably Lyons, the date 1510. Like other similar works, this contains the "Libri afforismorum domini Ypocratis", in Latin, translated from the Greek by Theodorus Gaza, "medicus". Some of the Introductions had the title "Articella", or "Artisella", from the fact that they contained the "ars parva" of Galen, also called the "Techni" or "Tegni" in various copies, and not from "Articella" as sometimes thought. "Artisella" was the title of a Venetian imprint of 1491. Dr Crummer has a good example printed in Florence in 1534.

That remarkable character, Suidas, a Greek biographer and lexicographer, who lived in the end of the tenth century, spoke of the Aphorisms as surpassing the human mind. An Arab version bearing the date 1100 A.D. is thought to have been the most ancient manuscript on linen paper, parchment and papyrus having been used before. The statement shows how scholars habitually ignored the Chinese, for they used paper from the second century, B.C. The Arabs came into

possession of some in 751, when a Chinese army attacked Samarkand, and paper-making then spread all through Arabic lands and thence to Europe. It is said that the oldest recorded Western document on paper is a deed of King Roger of Sicily, in 1102.

Constantine, called the African, one of the ornaments of the School of Salerno, where he became a monk, translated the Aphorisms with the Commentaries of Galen into Latin late in the eleventh century, this being the first work of Galen to be put into Latin. Rabbi Moses Maimonides, born in Cordova in 1135, called The Great Maimonides, and better known as philosopher and Talmudist than physician, included in his writings a Commentary on the Aphorisms.

How vital the Aphorisms were in the education of the medieval medical student we can see by a conspicuous example. John of Gaddesden, supposed by some to have been the original of "The Doctour of Phisyk" of the "Canterbury Tales", studied medicine at Oxford about 1303. For "inception in medicine", which apparently included the taking of the B.M. degree at that time, he had to have read one book of Galen or one book of the Aphorisms of Hippocrates. So well did John study the aphorisms that he quoted them one hundred and twenty times in his great work, the "Rosa Anglica", written in 1314. A System of Medicine "from head to feet", this was widely used in manuscript in the fourteenth and fifteenth centuries. There are three copies in the British Museum; one, dated 1356, in the Bibliothèque Nationale in Paris, and one

each in the Bodleian and in Merton College library. It was printed in 1492 (Pavia), 1502 (Venice), 1517 (Pavia), 1595 (Augsburg)*. The "Surgery" of Guy de Chauliac, father of French surgery and most celebrated surgeon of the middle ages, first published in 1363, also shows familiarity with the Aphorisms. In the great medieval medical schools of Salerno and Montpellier, Hippocrates and Galen were the two authors whose works were especially studied. Salerno, indeed, was called *Civitas Hippocratica*.

Two and a half centuries after Gaddesden, we find the youthful Felix Plater, who became one of the best observers and one of the most judicious writers of the sixteenth century, studying for the doctorate in Basel. When he took his final examinations in 1557, he was called upon to explain, among other questions, an aphorism of Hippocrates, (the first in section three) reading "*Mutationes temperum pariunt morbos*"**. Another century later, about 1647, Sir Thomas Browne advised a correspondent "that Hippocrates' Aphorisms should be conned for the frequent use which may be made of them" (Pickering Ed, 1836).

The editions of the Aphorisms before 1500 are not accurately known. After 1500, and including those in "Complete Works" of Hippocrates and of Galen, in *Isagoges* and *Articellae*, the number is so large that some

writers think the Aphorisms have been printed oftener than any other profane work. A-J-L Jourdan and F-G Boisseau, in the *Dict des Sci Méd*, *Biographie Médicale*, *Art Hippocrate*, T 5, Paris, 1822, give forty editions between 1532 and 1800.

J-E Dezeimeris, *Dict Hist de la Médecine, anc et mod* T III, Paris, 1836, gives a still larger number of editions, including many incunables, and also including *Articellae*, and combinations of various works, Hippocratic and others, with the Aphorisms. He mentions fourteen French versions up to 1835, and 27 versified paraphrases, chiefly Latin. The number of Commentaries on the Aphorisms, as Dezeimeris says, is immense, and he names many in his very interesting article. The greatest number of "Aphorisms" I find in a single list is that in the Catalogue of Printed Books of the British Museum, 1889, viz, 134 editions of the Aphorisms as separate works. Many languages are represented including Greek, Arabic, Latin, Italian, Spanish, Hebrew, English and French. Of Greek and Latin texts, there were 13 in the sixteenth century, 19 in the seventeenth, 6 in the eighteenth, 1 in the nineteenth. Greek and English, one in 1831. In Latin only, 5 in the fifteenth century, 29 in the sixteenth, 29 in the seventeenth, 10 in the eighteenth. Latin and French 3 in the seventeenth century. French only 1557, 1660, 1685. Italian only 1621; English 1550, 1585, 1610, 1655, 1663, 1708, 1735. In German, 1825, 1840. An Arabic text of *Humay ben Ishak* was printed in Calcutta in 1832. But this number is incomplete and an effort to correct it from bibliography is

*H. P. Cholmeley, *John of Gaddesden and the Rosa Anglica*. Oxford, 1912.

**Brief Notes on Felix Plater with Extracts from his *ms. Memoirs* preserved in the Library of Basel. By C. G. Cumston. Johns Hopkins Hosp. Bull. April, 1912.

does not seem worth while. The many versified translations suggest that it was probably a popular pastime in the early years of the revival of learning to turn the Greek prose into Latin verse, or rarely a modern language. The places of publication include all the well-known seats of printing. The number of editions depended to a great extent on the free-trade in printing, especially that dealing with copies of the classics, in the original tongues as well as in Latin translations.

In size, we have everything from quarto to 32mo, pocket sizes being numerous from the earliest printing. The editors include all the great restorers and commentators of Greek medicine. One of the most celebrated, although better known at present as a comic writer than a medical guide, was Francois Rabelais, the biographer of Gargantua and Pantagruel. His talents were well known to his contemporaries. Familiar with Greek, Latin and Arabic, made bachelor at Montpellier in 1530, he lectured on Galen and Hippocrates in 1531. Dr A. F. Le Double (Rabelais Anatomiste et Physiologiste, Paris, 1899) has shown the extent and accuracy of his anatomical knowledge. Gargantua began to appear in 1533, but in the preceding year Rabelais had published a Greek edition of the Aphorisms, and in 1543 and 1545 he published Latin versions of the latter from the translation of Nicholas Leoniceus. Dr LeRoy Crummer has a very fine example of the very rare Ionic text (1532), bound with the Aphorisms (1545) and three other Hippocratic chapters and the Ars medicinae of Galen. Many of the editions of the sixteenth and seventeenth

centuries included the Commentaries of Galen. A careful study of the latter might explain the disinclination to original work so evident in students of those days. Besides the seven sections of Galen, almost universally followed, there was sometimes an eighth, containing Aphorisms thought to be apocryphal.

The lack of classification is remarkable, and Dezeimeris rearranged the Aphorisms according to a simple clinical classification, which I shall follow in making some selections, using the edition of 1841. The English text of Francis Adams (Sydenham Society, London, 1849), the scholarly surgeon of Banbury, the French of E. Littré (Paris, 1844), and the German of Robert Fuchs (Munich, 1893) are convenient for modern readers.

My early studies of the Aphorisms



FIG 1 Title page of 1545 Aphorisms, edited by Rabelais, from specimen in the collection of Dr LeRoy Crummer

FIG 2 First page of Ionic Greek text of the Aphorisms, edited 1532 by Rabelius bound with No 1 and other Hippocratic writings

English literature of medicine has proved a complete failure"

Of the numerous definitions of an aphorism, I think one of the best is Adams' version of Galen's, viz, "a writing remarkable for brevity and point". Brevity is a constant feature of the Hippocratic writings, and in the Aphorisms this has been carried so far

that none of the commentators has been able to follow the example. As to the object of the work, I accept the suggestion made by many others, that it was intended to be a comprehensive treatise on the physical science, physiology and medicine known at that time. This explains the inclusion of the aphorisms about seasons,

COMMENT. DE GAL.

Ce que cy apres sera dit dedans ce livre des Aphorismes. I. Breche.

APHOR. I.

Vita brevis, ars verò longa, occasio autem preceps experimentum periculofum, iudicium difficile. Nec solum seipsum præstare oportet opportuna facientem, sed & ægrum, & affidentes, & exteriora.

*La vie est briefue, mais l'art est longue, l'occasion est soudaine & legerement passe, l'experience perilleuse & dangereuse: le iugement difficile. Et ne se faut seulement mon-
strer faire bien son deuoir: mais aussi faut que le patient face de sa part ce qu'il doit, & les ministres & seruiteurs qui sont autour de luy soient tels qu'ils doiuent estre: & que les choses exterieures soient conuenables, & ainsi qu'il appartient.*

Gal. Il est tenu pour certain, presque entre tous les expositeurs, que ceste oraison, soit qu'elle fust en vn, ou plusieurs Aphorismes, est le proème & prefation de tout l'œuvre. Mais ce n'est

I MEYANII
 O' EIO' BEXYCTE, H O' TEGH' MA-
 KPH, O O' KAPDZ OZYE, H O' THES
 CPOBPH, H O' KEIOTE' XHMEPI. ΔH O
 O' MOYON' EYOTIN' APETEIXIN TA ΔIOYTA
 * ΠOIOYNTA, AΛΛA K' O' TOCIOYTA, K' TIS
 APETEINTA, K' TA' XWOTI.

1. Vita 2 brevis, 3 ars verò 4 longa Sed 5 occasio momentosa [& magni momenti,] 6 empirica periclitatio 7 periculosa, 8 iudicium 9 difficile. Neque verò 10 Medicus modò sic comparare se debet, vt faciat quod factò opus est Sed & 11 æger, & qui præsto 12 sunt, & quæ foris 13 incidunt.

Hortatur nos hoc Præmissis, ut tempus & diligenter adhibeamus ad hanc artem.

Vita quid
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Ultracelino

Σελίδα 119 από 120



OFFICINA DEL TIPIGRO,
KATHOLIKEN-STRASSE,
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FIG 6 The First Aphorism from No 5
Compare the Greek text with that of No 2

ly work, and perhaps be led to a more serious study of other chapters of ancient medicine

The First Aphorism serves as an Introduction, or Prolegomenon, in the edition of Dezeimeris, and as I wish to give it special attention I pass on to another often alluded to (Section II. Aph 22) · "Diseases which arise from repletion are cured by depletion, and those that arise from depletion are cured by repletion, and in general diseases are cured by their contraries." This is sometimes mentioned as the original "contraria contrariis curantur."

ur", but the idea is better expressed in another Hippocratic work "On the Places in Man" It does not seem to require any discussion now Under the sub-title, "The Art of imitating the curative processes of Nature", we find, I 21 "Those things which require to be evacuated should be evacuated, wherever they most tend, by the proper outlets". Cosmetics and general prognosis join in II 54 "Largeness of person in youth is noble and not unbecoming, but in old age it is inconvenient and worse than a smaller stature" Signs of imminence of disease may be represented by II 5 "Spontaneous lassitude indicates disease" Uroscopy has eight aphorisms relating to it, VII 34 being one of the most interesting "When bubbles settle on the surface of the urine, they indicate disease of the kidneys" If this means bubbles that remain after shaking the urine, from albumin in the latter, we can only wonder how such knowledge can be explained without experience with autopsies It seems to represent a different kind of observation from that in II. 33 "In every disease it is a good sign when the patient's intellect is sound, and he is disposed to take whatever food is offered to him, but the contrary is bad" Equally sage is II 19 "In acute disease it is not quite safe to prognosticate either death or recovery" And II 42 "It is impossible to remove a strong attack of apoplexy, and not easy to remove a weak one". In V 10, we may not agree with the time element, but the general thought is suggestive "Persons who escape an attack of quinsy, when the disease is turned upon the lungs die in seven days; or if they pass these they become affected with

empyema" That Hippocrates was far in advance of his time in his knowledge of pleural disease is generally known A good example is shown in VII 44 "When empyema is treated either by the cautery or incision, if pure and white pus flows from the wound, the patients recover; and if mixed with blood, slimy and fetid, they die" VI. 27 "Those cases of empyema which are treated by incision or the cautery, if the water or pus flows rapidly all at once, certainly prove fatal" An interesting statistical observation is given in V 9 "Phthisis most commonly occurs between the ages of eighteen and thirty-five" V 12 is not so clear "Phthisical persons, the hair of whose head fall off, die if diarrhoea set in"

HIPPOCRATIS APHORISMI.

PROLEGOMENA

Amplitudo — difficultates — subsidia artis

1 *Vita brevis, ars longa, occasio preceps, experientia fallax, judicium difficile Nec solum seipsum oportet prestare opportuna scientiam, sed et regnum et assidentes et exteriora* Sect 1, aph 1

MEDICINÆ DEFINITIO

α *Artes curandi contraria contrariis*

2 *Quicumque morbi ex repletionibus sunt, curat evacuatio, et quicumque ex evacuatione, repletio et horum contrarietas* Sect 11 aph 22

Conferantur et aph 19 sect 1, etc

FIG 7. From J-E Dezeimeris' *Résumé de la Médecine Hippocratique, ou Aphorismes d'Hippocrate classés dans un ordre systématique*, etc Paris, 1841

The doctrine of critical days is a serious difficulty in Hippocratic writings. A good example, in the sense that it is hard to understand, is IV 64 "When in cases of fever jaundice occurs on the seventh, the ninth, the eleventh, or the fourteenth day, it is a good symptom, provided the hypochondriac region be not hard. Otherwise it is not a good symptom." The very important doctrine of crises has a good example in II 12 "What remains in disease after the crisis is apt to produce relapses", but II 23 seems more dogmatic than useful "Acute diseases come to a crisis in fourteen days", unless we accept the explanation that we have here a definition of an acute disease. II 2 illustrates prognosis in a simple form "When sleep puts an end to delirium, it is a good sign", also, II 16 "When in a state of hunger, one ought not to undertake labor", and II 48 "In every movement of the body whenever one begins to feel fatigue, it will be relieved by rest", and II 4 "Neither repletion, nor fasting, nor anything else, is good when more than natural." II 21 has an appeal in these days of depression and secret ballots on Prohibition, "Drinking strong wines cures hunger", and II 11 belongs to it "It is easier to fill up with drink than with food." A good example of thoughtful medical observation is reflected in I 14 "Growing bodies have the most innate heat, they therefore require the most food, for otherwise their bodies are wasted. In old persons the heat is feeble, and therefore they require little fuel, as it were, to the flame, for it would be extinguished by much. On this account, also, fevers in old per-

sons are not equally acute, because their bodies are cold." There are many aphorisms on diet. I 4 reads "A slender and restricted diet is always dangerous in chronic diseases, and also in acute diseases, where it is not requisite." And again, "A diet brought to the extreme point of attenuation is dangerous, and repletion, when in the extreme, is also dangerous." II 38 shows a diplomatic method still useful in practical dietetics "An article of food or drink which is slightly worse, but more palatable, is to be preferred to such as are better but less palatable."

Therapeutic directions are numerous and varied. II 37 reads "Purgative medicines agree ill with persons in good health." Hellebore, which many of us have never had occasion to prescribe, played an important part in ancient Greek medicine. We find it in IV 16 "Hellebore is dangerous to persons whose besh is sound, for it induces convulsions" and V 1, "a spasm from taking hellebore is of a fatal nature", but IV 15 "When you wish the hellebore to act more, move the body, and when to stop let the patient get sleep and rest."

Bleeding, of course, was much in use, and the advice in VI 47 "Persons who are benefitted by venesection or purging, should be bled or purged in spring", was widely observed until late in the last century. The same advice, without the purging, was repeated in VII 53. The rules about purging are extensive. IV 5 says "About the time of the dog-days, and before it the administration of purgatives is unsuitable." Adams tells us

that this rule was followed by all the Greek and Arab physicians. According to Galen, it is fighting against nature to determine inwardly by purgative medicine, while the heat is determining outwardly. Even now I think we are not agreed upon the advice in I 24 "Use purgative medicines sparingly in acute diseases and at the commencement, and not without circumspection"

Aphorisms dealing with surgical problems are numerous and interesting, but I shall give only a few. VI 6 "A severe wound of the bladder, of the brain, of the heart, of the diaphragm, of the small intestines, of the stomach, and of the liver, is deadly" Galen points out that the word "deadly" is often used in the sense of "very dangerous" VII 14 says that "stupor or delirium from a blow on the head is bad" VI 8 "In dropsical persons, ulcers forming on the body are not easily healed" VI 38 "It is better not to apply any treatment in cases of occult cancer (meaning either not ulcerated or deep-seated), for if treated the patients die quickly, but if not treated, they hold out a long time" IV. 79 "In those cases where there is a sandy sediment in the urine, there is calculus in the bladder or kidneys", Galen added the words "or kidneys", saying they were not mentioned in the copies of the Aphorisms then in use. A belief still encountered is shown in VI 12 "When a person has been cured of chronic hemorrhoids, unless one be left, there is danger of dropsy or phthisis supervening"

Gynecology and obstetrics are freely represented. V 50 "If you wish to procure menses in a woman, apply as

large a cupping instrument as possible to the breasts" V 42 "A woman with child, if it be a male, has a good color, but if a female, she has a bad color", raises many questions about the accuracy of observation, while V 38 clearly goes back to the very old belief in the uterus as a two-chambered organ, it reads "If, in a woman pregnant with twins, either of her breasts lose its fulness, she will part with one of her children; and if it is the right breast which becomes slender, it will be the male child, or if the left, the female" By the time of Galen the error had been recognized V 49 is interesting ethnologically, because Adams tells us the practice was popular in the North of Scotland in his time, about one hundred years ago. The Aphorism says "To procure the expulsion of the secundines, apply a sternutatory, and shut the nostrils and mouth"

The First Aphorism is in two sentences, which I shall consider in the reverse order, for the second sentence forms a fitting introduction to the technical aphorisms that follow. It reads, in Adams' translation "The physician must not only be prepared to do what is right himself, but also to make the patient, the attendants, and externals cooperate" This reveals a wise and experienced physician who knew well one of the most important parts of the practice of his art. He knew the votary of the Old Medicine, who had left his crutch and his votive offering in the Esculapian temple, he knew the solicitous relatives, from grandmother down, the fussy neighbors, with recommendations from the market place, the theater and gym-

nasium, and the advocates of all the cults, and he avoided all discussion and argument in one apodictic sentence. The beginning of the Aphorism is also, I think, best rendered in English by Adams, as follows "Life is short, and the Art long, the occasion fleeting, experience fallacious, and judgment difficult." The opening words have arrested the attention of some of the most acute minds in all the ages. Cicero, Horace, Seneca, Pliny the Elder, Juvenal, Martial, Sallust, and other Roman writers knew them. Molière used the first part of the aphorism in a medical comedy, "The Flying Doctor." Goethe quoted "Life is short, Art long" twice in the First Part of "Faust." Longfellow's use of the words in the "Psalm of Life" is well known. Daremberg, the learned medical historian said "The beginning of the Aphorisms has an incomparable majesty. It is impossible to imagine expressions so brief and so striking for describing the grandeur of Medicine and the responsibility of the physician." In the original Greek the Aphorism is even more concise than is most translations, as the Greeks omitted verbs, so that we might read "Life short, but the art long" etc. It is an interesting proof of the practical value of the Greek language that of the ten chief words in the first half of the Aphorism, seven are in daily use in English words like biology, brachycephalic, technic, macrocosm, empiricism, oxygen, and crisis, and two others are used in chemistry. It is hardly necessary to say that all medical commentators hold that "Art" means the Art of Medicine. The context makes this clear, but no medical man can object

to the more general application, as by Goethe and Longfellow.

The next phrase, "Occasion fleeting" deserves comment. The word used for occasion means not time in a general way, but "fit", "proper", "exact or critical time", "time in reference to subject". It corresponds to the Latin "opportunitas". The word for "fleeting" is literally "sharp," "pointed", "cutting", "vehement", "prompt", "fleeting".

It is easy to see from this alone the keen therapeutic sense of the author. We can understand how it was that he seized the time for opening an empyema, and we can imagine how his mind would have appreciated the exigent medicine of today, with a perforated peptic ulcer, an acute appendicitis or an empyema of the gall-bladder, a twisted pedicle, a tumor of the spine, or a meningitis. Yet the needed promptness runs a risk at present of being missed by reason of the technical details that seem necessary and that can be done more rapidly if promptness is realized as essential. I often think how applicable a certain saying attributed to Napoleon is in such cases. It is said that after an early Italian battle the opposing commander asked for an armistice in order to improve his position. Napoleon with more oratory than Grant on a similar occasion, said "No", adding "It may happen that I shall lose battles but you will never catch me losing minutes, either by overconfidence or sloth. In converting Greek into medieval Latin there were some difficulties. 'Occasio' that is, 'opportunity', 'fit time', or 'favorable time', is nearly always used by early editors but 'fleeting' is

was used by Hugo of Siena (d 1439) in a Venice, 1498, edition (Osler Library, No 171), and in the Florence Articella of 1534. It also appears in the Van der Linden edition, Lugd Batav, 1665. "Acutum" was used for the 1498 and 1534, "praeceptum" for the 1665. Praeceptum, "headlong", "sudden", was the adjective most frequently following "ocasio", but "celeris", and "volucris", "fleet", are also used. Heurnius, 1543-1601, who edited many editions, was not satisfied with such simple language and said "Ocasio momentosa & magni momenti". A few editors introduced a "nevertheless" into the phrase. English, French and German editors followed the general ideas, and we find "occasion sudden", "l'occasion echappe" (Le Clerc, 1702), "l'occasion passe vite", "l'occasion prompt a echapper", "l'occasion fugitive", and "rechte Augenblick", "Gelegenheit fluchtig", "schnell vorübergehend", "plotzlich". Dr Eliot used "occasion instant" in the inscription for one of the Harvard Medical School buildings, an unusual word equivalent to "urgent". (See Second Epistle of Paul to Timothy, Rev vers 4 2 "be instant in season, out of season".)

The next clause, "experience fallacious", has caused more difficulty to translators than any other part, and furnishes an interesting study. "Experientia fallax" is a frequent Latin term, and can be traced back to soon after 1500, but "experimentum fallax" is older, i.e., 1498 (Hugo de Seno). While we now distinguish between "experiment" and "experience" that was not always so. The words come from "Peira", and

when we test this word by its early use, we find that it indicates such things as trial, attempt, undertaking, thing to be proved, and so makes the basis of the old and modern word empiricism. It often included attempts the outcome of which might be uncertain. So it was used for a trick, a stratagem, hence a robbery or piracy; a temptation, in ecclesiastical writing, an attempt to seduce a female, an action by sea, and so on. The qualifying adjective, translated "fallacious", means more frequently "slippery", or "likely to cause a slip, fall or hurt, insecure, doubtful, delusive, perilous, reeling, unstable".

Galen recognized the point of weakness in the phrase, and commented at considerable length, but also with some obscurity. It seems clear that he meant that therapeutic experiment is dangerous, because it may involve the life of a human being. But we must understand the position of therapeutics at the time, with its division into sects, the Methodists who relied upon theory, the Empirics, who tried experiments, and the Dogmatists, who took a middle course. Evidently the Hippocrates who objected to the routine use of hellebore was not the same who incised the empyema. In the former case he was probably right in withholding the drug, but in the latter he was trying the "dangerous experiment" of operation rather than leaving the patient to die according to rule. If the incision did not heal, and the patient had what we now recognize as a tuberculous empyema, Hippocrates might well have said "experience fallacious". Then as now, different degrees of faith in rules affected one's

practice Guy of Chauliac with Gallic keenness read that part of the aphorism, "experience fallacious and dangerous" As printing went on "experimentum periculosum" was preferred, and "experimentum fallax" rare, and "experientia periculosa" almost disappeared, reviving in 1829, while "experientia fallax" disappeared and reappeared in a similar way In the Foes-Plant edition of 1633 (Lugd.) Foes preferred "experientia fallax", while Plant chose "experientia periculosa" Heurn, who had to make matters more emphatic, introduced "empirica perichitatio periculosa" (1601, 1609, 1627, 1633) Even before the experimental age was conscious of its surroundings, the question of interpretation had to be considered, and so we find Paracelsus making a characteristic pronouncement For a copy of this I have to thank Dr W W Francis It is taken from No 177 of the Osler Catalog Except for Paracelsus specialists it would be too long to quote in full Paracelsus states that "in the beginning" there was no Theory, but only Experience "this loosens, that constipates" "Scientia ist nimmer Experimentum fallax das macht die Theorika medica. etc"

Dr Francis has also found an interesting comment in the "Medicina Hippocratica exponens Aphorismos Hippocratis" Auctore Johanne de Gorter Ed Prima Italica Patavii 1747 From this it seems that de Gorter distinguished between experiment and experience, and went on to say "Not every experiment is perilous, for many physicists and chemists have made many experiments, in which there was no peril But in medicine

an experiment is perilous, for the end of a rash experiment is death" Modern languages, of course, give only a reflection of the perplexities of the earlier Latin writers So we see that in Le Clerc in 1702, Dezeimeris in 1841, and Littré in 1845 "trompeuse" is used to describe "l'experience", Daremberg put it "l'empirisme est dangereuse" The Germans began later, and followed the same lines J F C Grim, 1837 "Erfahrung truglich", Fuchs, 1895 "Versuch truglich", Kurt Sprengel, 1789 "Erfahrung misslich", J A Petschaft, 1825 "Der Versuch gefahlich"

The English translation of Sprengel of 1708 is very crude and puts the phrase "to make experiments dangerous" An early English edition, anonymous, the Preface signed "S H" London, 1610 puts it "experience uncertain". It was a refreshing variation when Francis G Benedict took President Eliot's version and made "experiment" an experiment in the modern way, not a therapeutic essay perhaps hundreds of years old, but a formal scientific procedure, gave a brilliant plea for the Aphorism as a guide "where the occasion for observation, for test or proving may exist but for a short time and the danger of not making the critical experiment at the proper time is indeed perilous" The recent discussion on "The Art and Human Nature" by Stewart R Roberts* gives eloquent testimony to the vitality of the aphorism as a guide to the Art in its clinical application

*Roberts Stewart R The Art and Human Nature New York Jr 1922 p 70-76

The last clause in the sentence, "judgment difficult", has come down in almost the same words in all the versions I have examined, "judicium difficile" (Lat.), "jugement difficile" (Fr.), "urtheilen schwierig" (Germ.) This is all the more remarkable since a simpler and more clinical meaning was near at hand. For the word "krisis", translated as "judgment" or "decision", involving choice or discrimina-

tion, also was used by Hippocrates for the crisis or critical stage of an illness. I find myself rejecting the latter interpretation "the crisis of a distemper", difficult, and agree with the more metaphysical interpretation given by so many others who have been puzzled and fascinated by the old but immortal medical theme "Life short, but the Art long, opportunity fleeting, experience fallacious, judgment difficult"

A Neglected Research

"MY SUGGESTION on this occasion [is] to initiate a thorough study of the problem of longevity in its special application to the medical profession. I feel strongly that a study of the lives, the habits and the recreations of, say, one thousand men of mark in the medical world for the last quarter of a century would make an extremely valuable contribution to knowledge. And this study should be amplified by research into all the more promising studies thus far made into the cause of death in the medical profession in this and other countries, with due regard to ages at death and the lessons to be learned from the countless instances of premature demise. Let guesswork and crude speculation be replaced by an authentic study of the salient facts, for it goes without saying that the nation suffers no greater social losses than that of the wasted years of life in the part of its medical men who die many years in advance of their attainable time.

"No career presents more strenuous mental effort, more exacting demands upon time, more sacrifice of means, more foregone leisure, than that of the doctor who takes his work seriously, and there are few who do not. No class of men renders a greater and more indispensable service to society than those who practice the art of medicine, in all its branches and selected specialists. Upon no group of men falls a heavier burden or a greater responsibility in peace and in war. And none has done more to advance the cause of a true civilization in which the blessing of a long life and freedom from illness and suffering is made the supreme test of its attainment on the part of an ever-increasing portion of mankind. Yet as I have shown, the evidence regarding its own health and longevity is decidedly disconcerting, while suggestive of neglect that justifies the inquiry suggested." FREDERICK L. HOFFMAN, LL.D., in *Life and Death in the Medical Profession*, 1932. The Prudential Insurance Company of America, Newark, New Jersey.

Editorial

NON-MEDICAL DISTRIBUTION OF DRUGS AND MEDICINES

The social, medical, and economic importance of the distribution and employment of drugs under other than proper medical direction is forcefully set forth in a recent publication* from The Committee on the Costs of Medical Care. In this report it is stated that the people of the United States spend each year approximately \$715,000,000 for drugs and medicines, of which only 27 per cent (\$190,000,000) is the portion expended for prescriptions, or for other purchases made with the direct advice of medical practitioners. This means that the public spends annually \$525,000,000 for self-medication in its various forms. The retail sales of home remedies account for \$165,000,000. These are usually bought without the express instruction of the medical profession, but may have been purchased at the suggestion and oftentimes with the approval of medical practitioners. The nation's bill for "patent medicines" comes to \$360,000,000. In the words of the Abstract of this publication (Number 14):

*The Costs of Medicines, The Manufacture and Distribution of Drugs and Medicines in the United States and the Services of Pharmacy in Medical Care, by C. RUFUS ROSELYN, Ph.D., C.P.A., and ROBERT P. FISCHER, B.S., Ph.D., University of Chicago Press, 268 pages, April, 1932. Price in cloth, \$2.50. Abstract obtainable from The Committee on the Costs of Medical Care, 910 Seventeenth St., N.W., Washington, D.C.

"Thus a total of \$525,000,000 is spent by the American people for medicines on their own initiative to cure minor or chronic ills which seem too trivial or too frequent in occurrence to warrant a call upon a medical practitioner, and to alleviate temporarily physical or mental symptoms which may or may not be the danger signals of serious disorders." The total amount spent for drugs and medicine is roughly of the same general order of magnitude as the sum spent for the services of physicians, or for hospitalization, and represents a charge, on the average, of between \$20 and \$25 per family per year. Since such purchases are made voluntarily by people who still have their earning capacity, and are distributed throughout the year, they have not been considered a burden and have not provoked unfriendly or critical discussion.

The "drug stores" of this country receive each year \$485,000,000 from the sale of home remedies and "patent medicines." The remainder of the expenditure for self-medication goes to mail-order houses, general stores, herbalists, itinerant vendors, etc. Aspirin, and sometimes more potent anodynes and soporifics, can be obtained in many restaurants and at soda fountains not connected with drug stores. One must have a good deal of sympathy for the pharmacist in the position in which he finds himself. If he conducts his business with conscientious regard to the ethical code of his profession, which decrees that he must not assume the functions and prerogatives of a physician,

cian by attempting to diagnose a customer's condition or by prescribing medicines for him, he does so in full knowledge that he is playing to the hand of a less conscientious competitor. At a time when the standards of education and experience which must be met in order to qualify for licensure as a pharmacist are being raised in many states, the whole tendency of pharmacology, therapeutics and pharmaceutical manufacture is such as to give the pharmacist less and less opportunity to practice the science of compounding medicines. He is forced to turn to merchandising, to catering, and to the art of salesmanship in order to secure economic independence. Although fewer doctors compound and dispense remedies from their offices, there is an increasing tendency for physicians to prescribe medicines already compounded under proprietary names. Judging by the advertisements which crowd many European medical journals, this tendency has reached a level on the continent which we may earnestly hope will never be approached here.

While the better type of druggist no longer stocks patent medicines for venereal diseases and deprecates over-the-counter prescribing for them, it is common knowledge that it is in connection with this group of diseases that the most flagrant disregard for professional ethics and public welfare exists. That which is 'common knowledge' is likewise supported by thoroughly controlled investigation. In the course of a survey* of the medical aspects of so-

*Survey by F. Snow, M.D., and Walter C. Snow, M.D. Medical aspects of social hygiene in San Francisco. *Jr. Social Hyg.*, 1931, 2: 25-27.

cial hygiene in San Francisco, questionnaires were filled in and returned by 130 drug stores. Of these, 79 per cent reported that 1,545 patients with disorders thought to be gonorrhea and 323 with disorders thought to be syphilis had applied for advice or for remedies during the month of July, 1931. Of the 102 druggists who stated what they did for those requesting such aid, 19 per cent admitted that they furnished remedies, 10 per cent furnished remedies occasionally, but in some instances referred them to a physician or clinic, 49 per cent always referred inquirers to a physician or clinic, and 23 per cent stated that they gave no information. As a check on the answers given, investigators visited 120 such establishments and gave a vague account of symptoms leading to an inference of the presence of venereal disease. The replies received indicated that 56 per cent of the drug stores visited were willing to undertake the illegal practice of medicine by diagnosing, or by prescribing, or both. Only 31 per cent definitely refused either to diagnose or to prescribe, and advised the inquirer to go to a doctor or clinic. Similar investigations have been conducted in several other cities. In Chicago, 63 per cent of the drug stores visited made diagnoses and offered to sell remedies or to treat syphilis or gonorrhea; in New Orleans, 34 per cent, in Washington, D. C., only four per cent. In addition, 445 young men of San Francisco were interviewed casually on the street and in barber shops and pool rooms to ascertain what they would do, or advise doing, if infected with a venereal disease. Thirty-six per cent advised going to a drug store

for aid, as compared to 23 per cent who would go to a physician and 18 per cent who would go to a clinic. There were six per cent who advised going to an herbalist or similar charlatan.

The extent to which the Chinese herb doctor, whose materia medica includes weird "remedies" of animal as well as vegetable origin, flourishes along the Pacific slope is almost beyond belief. The survey to which reference has been made revealed over 75 Chinese herb shops in San Francisco and vicinity alone. It is estimated that there are more than a thousand of them in this country. During the survey 12 herbalists were visited and all offered to sell remedies to "cure" syphilis or gonorrhea. "Six out of eight herbalists to whom letters were written diagnosed one of these diseases by means of the insufficient symptoms described in the letters and 'guaranteed' to cure by correspondence. The terms ranged from \$10 to \$50."

In the current telephone directory of one of the larger cities of the state of Washington there is displayed an advertisement which reads, in part, as follows: "Wing Wo Chinese Medicine Co., established 1899. Come in no matter what your ailment. The Chinese successfully use roots, herbs, barks, and berries for every ailment of mankind." Whether such concerns can be prosecuted under medical practice acts or not, it is extremely unlikely that the telephone company would in this instance continue such advertising if proper representations were made to it

by the County and State Medical Societies.

There are a number of ways in which the practitioner can do something to lessen this distribution of drugs without proper medical supervision. Here his personal interests are in such full accord with those of public welfare that he need not feel hampered lest his activities be construed as entirely self-serving. He should lose no opportunity to keep before his clientele and the lay public the fact, so much to their advantage, that the indispositions for which they undertake self-medication may be the manifestations of serious affections which require diagnosis in their early stages if they are to be cured or controlled. He should invoke the aid of, and lend his support to, those possessed of legal authority, as well as better business bureaus, and other agencies to secure the elimination of those practicing medicine illegally or making fraudulent promises of cure. Finally, he should secure in so far as possible, the sincere cooperation of pharmacists. He can demonstrate his appreciation of the problem facing the pharmacist by refraining from being a competitive compounder of medicines himself and by prescribing in such a manner as to make use of the professional knowledge and skill of the pharmacist, rather than depending largely upon medicines already compounded and sold under proprietary names. Both economically and therapeutically the patient should benefit by such a course of action.

Abstracts

Death Rates in a Group of Insured Persons (Public Health Reports, 1932, xlvii, 437-440)

Tables which can be found in the Statistical Bulletin of January, 1932, issued by the Metropolitan Life Insurance Company, provide an index, in advance of governmental figures, of the mortality status of the general population. They present the mortality experience of the industrial department of this company, by principal causes of death, for 1931 as compared with 1911 and 1921-1930, inclusive, and for December, 1931. The rates for recent years are based on between 17,000,000 and 19,000,000 insured persons in the United States and Canada. Although this is a more or less selected group and is largely urban, the death rate is a fair indication of the trend in the general population. In recent years the general death rates in this group have been averaging about 72 per cent of the death rate for the registration area of the United States. Six diseases, tuberculosis, diphtheria, whooping cough, pneumonia, diarrheal complaints, and puerperal conditions, recorded lower mortality rates in 1931 than ever before. The rate for typhoid fever equaled the minimal figure previously attained. The mortality rate for tuberculosis dropped 57 per cent in spite of the prevailing economic conditions. This is a larger decrease than the average year-to-year decline during the preceding decade, and the rate is 65.9 per cent lower than for 1911. Mortality from diphtheria showed a drop of 24.6 per cent in one year and of 50 per cent in three years. In spite of an incipient epidemic of influenza at its beginning, the year ended with a new minimum for the death rate from this disease. The death rate for diseases of the respiratory tract and childbirth showed a decline of 23 per cent for this group as compared with 1911. Part of this decline is due to the fall in the birth

rate. That some of the reduction is real can be demonstrated by computing the rate on the basis of live births. New minimal death rates were recorded for accidental burns and for injuries in railroad accidents, and rates lower than those in 1930 for alcoholism and chronic nephritis. On the other hand, an increase of 7.4 per cent appeared in the death rate for cancer in 1931. While the death rate for diseases of the heart is slowly rising, the increase is found in the older ages only. Diabetes recorded a new high rate, 14.4 per cent greater than in 1930 and 61 per cent above that of 20 years ago. Here the increase is in the age group past 45 years, and particularly among women. The mortality from automobile accidents increased more than five per cent over the rate for 1930. For this cause of death there has been a rise of almost 900 per cent in 20 years, and it is estimated that not less than 34,000 people lost their lives in automobile accidents in the United States in 1931. The Bulletin upon which this article is based states that "as yet there has not been any appreciable injury to the public health from the economic conditions that have prevailed."

[Editorial Comment. As has been pointed out previously in the editorial columns of the ANNALS, the reasons why present economic conditions have not produced a recognizable deleterious effect in respect to mortality and morbidity are multiple. Even in economic depression itself there are positive and negative public health factors, the algebraic sum of which is not easily determinable. After all, study of such statistical analyses as that of the paper here abstracted, leaves the firm impression that the chief factor in lowering mortality rates has been the progress which Medicine has made in the prevention and treatment of those diseases which take their heavy toll before the middle period of life. Rising mortality rates for the so-called degenerative dis-

eases must be expected, since all must die. Life-savings at one end of the scale must be balanced by life-losses at the other, for preventive medicine can neither bestow immortality nor appreciably alter the histogenetic life limit imposed upon human protoplasm by the evolutionary processes of millions of years. Rather may we not expect that the proportion of those past middle life who will attain extreme old age will decrease, since there will be preserved to reach that group some who are intrinsically less resistant? One must view with apprehension the rapidly rising list of automobile casualties, preventable for the greater part, and yet taking an annual toll from all walks of life, including those best fitted to render significant service to the race. Our own profession pays a heavy tribute to this cause of death.]

Cirrhosis of the Liver By FRANK B. MALLORY, M.D. (New Engl. Jr. Med., 1932, ccvi, 1231-1239)

Among 9346 autopsies performed at the Boston City Hospital during the past 35 years there were found 550 examples of well-marked hepatic cirrhosis, an incidence of 5.88 per cent. These were classified as follows:

Alcoholic cirrhosis	270	48.90 per cent
Pigment cirrhosis	49	8.90 per cent
Healed acute yellow atrophy	46	8.36 per cent
Syphilitic cirrhosis	28	5.09 per cent
Colon bacillus cirrhosis	25	4.54 per cent
Obstructive cirrhosis	24	4.36 per cent
Obstructive and colon bacillus cirrhosis	3	0.54 per cent
Cancer cirrhosis	1	0.18 per cent
Not classified	104	18.90 per cent

It was found that healed acute yellow atrophy and syphilitic cirrhosis may occur at any age but alcoholic cirrhosis and pigment cirrhosis are practically limited to adult life and cause death at a late age, indicating that these latter lesions require many years for development. The incidences of ascites, jaundice, esophageal varix, hemorrhage and of various degrees of enlargement of the spleen are given for each

type of cirrhosis represented in the series. Enlargement of the spleen with increase in stroma elements was of frequent occurrence and is directly due to the obstruction to the flow of portal blood through the liver. Twelve examples of primary liver cell cancer were encountered. Four of these were in association with pigment cirrhosis and three each with alcoholic cirrhosis and healed acute yellow atrophy. Obstructive cirrhosis is caused by occlusion of either the hepatic or common bile duct. There results a slight to considerable sclerosis around all of the bile ducts, producing a smooth to finely granular cirrhosis which is commonly called biliary cirrhosis. The cirrhosis produced by an ascending colon bacillus cholangitis likewise involves the bile ducts and the immediately surrounding tissues. If any type of cirrhosis should be recognized as Hanot's, it would seem to be the early stage of this. [The editor has thought that diffuse congenital syphilis in an adult liver more nearly meets the conception of Hanot's cirrhosis.] It seems probable that in addition to the well-known group of toxic substances, capable of producing acute yellow atrophy of the liver, the direct action of a streptococcus must be added in considering the etiology of this important form, which is so frequently missed in clinical diagnosis. Pigment cirrhosis forms the first and most important lesion in hemochromatosis. It is characterized by the presence of two pigments in the liver cells, hemofuscin derived from hemoglobin and hemosiderin which is slowly developed from the hemofuscin. Pigment cirrhosis can be produced in rabbits, sheep and monkeys by means of chronic copper poisoning in 6 to 12 months provided the dose is large enough. In man as far as can be ascertained from clinical observations, well-marked pigment cirrhosis requires in the neighborhood of fifteen years for development. The chief sources of chronic copper poisoning are to be found in the copper coils used in distillation apparatus. It was made from pyrites in which copper containing material had been sprayed and in operation as a result of the cutting grinding and polishing of the coils and brass. As to alcoholic cirrhosis, experimental evidence is recent that the

being the cause of this lesion. The essential histopathological lesion, hitherto not generally recognized, involves the development of minute hyaline droplets within the cytoplasm of the liver cells. These droplets fuse to form an irregular hyaline meshwork about the nuclei. There is some experimental evidence that a similar basic lesion is produced by phosphorus, so that the suggestion is made that this substance may be the cause of so-called alcoholic cirrhosis. However, the presence of phosphorus in alcoholic beverages has not been demonstrated as yet so that certain desirable links in the chain of evidence are still missing.

Auricular Fibrillation Ambulatory Treatment with Quinidine By S. A. WEISMAN, M.D. (Arch Int Med, 1932, xlix, 728-734)

This article deals with 24 patients with auricular fibrillation who were treated by the ambulatory method with quinidine sulphate in the outpatient department of the University of Minnesota. All patients were first given digitalis. If the heart is decompensated the patient is well digitalized until there is evidence that the heart is fully compensated, or nearly so. Quinidine is then given in small doses: 0.1 gm on the first day, 0.2 gm on the following day, and on the third day, 0.4 gm. For five days this dose is maintained, with 0.1 gm taken every two hours. At this point the digitalis may be reduced or discontinued. On the seventh day the dose of quinidine is increased to 1 gm per day (5 grains every two hours until three doses have been taken). Later the amount may be increased to 20, 30, or even 40 grains per day, always given in divided doses at two hour intervals. As soon as cardiac rhythm becomes regular the dose of quinidine is reduced, and a maintenance dose is established. This may be 5 grains daily, or 5 grains every other day. Normal rhythm was restored in 17 of the 24 cases treated,

that is, 70.8 per cent. Eighteen of the 24 patients were 50 years of age or over, in 14 of this group, 77 per cent, the heart was restored to normal rhythm. Regular rhythm was restored, also, in three of the remaining six. Those with hypertension seemed to respond more quickly than the rheumatic group. Two accidents occurred during treatment: one death from coronary thrombosis, and one case of hemiplegia.

A Case of Friedlander's Pneumonia By E. H. BENSLEY, B.A., M.D. (Canad Med Assoc J, 1932, xxvi, 681-684)

The patient, an adult, white male, 42 years of age, was well until three days before admission to the Montreal General Hospital. On rising in the morning, he had vomited, soon suffered from headache, and had chills, warm flushes and sweats, cough, and expectoration. The temperature ranged between 101.4° and 104.4°, and signs of consolidation appeared at the left base on the day following admission. The patient's condition became steadily worse and he died 38 hours after admission to the hospital, on the sixth day of the illness. At autopsy, the entire upper lobe of the right lung and large portions of both lobes of the left showed consolidation. From the cut surface of the solid areas, a large amount of mucinous greyish purulent material was exuded. Microscopical examination showed considerable numbers of large mononuclear cells as well as polymorphonuclear leucocytes in the alveoli. Red cells and fibrin were less prominent in the exudate than is usually true of pneumococcal pneumonia. The Friedlander's bacillus was obtained from three sources in this case—the sputum (ante mortem), ante mortem blood culture, and post mortem blood culture. A white mouse, inoculated intraperitoneally with washed sputum, yielded pure cultures of Friedlander's bacillus from the heart's blood and the peritoneal exudate.

Reviews

Cancer What Everyone Should Know About It By JAMES A. TOBEY, Dr P H, Fellow, American Public Health Association, Associate Fellow, American Medical Association, Member, American Society for the Control of Cancer With introductions by JOSEPH COLT BLOODGOOD, M.D. and H. L. MENCKEN 323 pages with 17 illustrations Alfred A. Knopf, New York, 1932 Price, \$3.00

Cancer, What Everyone Should Know About It, is written, as the title indicates, particularly to inform the laity about cancer. The author has taken pains to explain all medical terms and procedures in detail. Dr. Tobey describes the nature of cancer and gives its history throughout the ages. A chapter is devoted to brief life stories of famous persons who had cancer, as the Bonaparte family, Presidents Grant and Cleveland, and many others. In giving the types and locations of cancer it is stated that cancer of the stomach is the most serious form of the disease, causing about one-third of all deaths from cancer. He believes it to be as curable as any other form when an early diagnosis is made. More frequent gastrointestinal X-ray examinations are advocated in all cases of chronic dyspepsia in the hope of reducing the mortality of cancer of the stomach.

"Danger signals of all cancers can be summarized in these words:

1. Any lump in the breast or other part of the body, especially one which begins to grow or change,

2. Any sore that does not heal particularly on the face or mouth,

3. Any unusual discharge or bleeding from any part of the body. Pain, it should be remembered, is always one of the later symptoms."

In regard to treatment

"No member of any of the healing cults outside the pale of regular medicine is capable

of giving proper treatment for cancer, and faith healing is worse than nothing." He emphasizes that there is no serum nor vaccine, no salve, plaster or paste and no chemical, except radium, which had been proven to alleviate cancer. In regard to irradiation, x-ray or radium, he states that "it cannot surpass surgery in many instances, and in others it is only a supplement to it, but in numerous cases it is an effective substitute. He gives an interesting review of the history of x-ray and radium, particularly Madame Curie's life and work. Dr. James Ewing is quoted as to the heredity of cancer, whose view, in brief, is that the hereditary influence does not convey the disease but only structural peculiarities rendering certain organs especially prone to cancer. Dr. Maude Slye's work and Dr. Warthin's cancer family are also described. The author makes it clear that contagion plays no part in the causation of cancer and repeatedly warns against quack cancer cures, telling at length of the evils of "The Great American Fraud." He advocates surgery, x-ray and radium as the only known treatment of cancer. The whole message is one of hope and cheerfulness. The author feels that cancer is largely preventable with proper knowledge, and curable if diagnosed and treated early. But how very often it is impossible to make an early diagnosis, because of inaccessibility and lack of definite findings! But to err in the direction of optimism may not be altogether a fault in a book intended for intelligent laymen.

R. C. W.

Applied Pharmacology By A. I. CLAY, M.C., M.D., F.R.C.P., F.R.S. Professor of Materia Medica and Pharmacology at the University of London, formerly Professor of Pharmacology at the University of Cambridge and at the University of London. Published by

590 pages, 72 illustrations P Blakiston's Son and Co, Inc, Philadelphia, 1932 Price, \$4 00 net

This edition of *Applied Pharmacology* follows its predecessor after an interval of but two years. This has been necessary in order to incorporate the recent advances in therapeutics. This book differs from the purely academic presentation of Pharmacology in an effort to bridge the gap which is too often widely existent between that science and therapeutics. Thus we find the subject matter arranged, for the greater part, according to organs and systems with a view to function, rather than with regard to the origin or nature of the medicinal agents themselves. Throughout, the aim has been to present such actions of drugs as are capable of scientific demonstration. There are certain minor changes which, in the next edition, would increase the usefulness of this book. Some point is made of the relative costs of drugs, but these values are in English currency requiring the American reader to transpose to terms with which he is more familiar. It is questionable whether a chapter of but 17 pages covering all forms of radiations is worth including or even germane to the subject covered by the title. Although familiar with the work of Aub and his associates, the author seems to have missed the point (page 538) that the most effective treatment of some forms of lead poisoning is to promote lead fixation, as contrasted with lead elimination. The index has not kept up with the revision. Although the text includes a paragraph on ephedrine the index does not refer to that drug. Aside from such minor faults, this is a very useful book, well-printed and unusually free from typographical errors.

United States Army X-Ray Manual Second Edition. Rewritten and Edited by LT. COL. H. C. PETERSKY, MC USA. 500 pages, 224 ill. Paul B. Hoeber, Inc., New York City, 1932. Price in flexible binding \$5 00.

The second edition of this book was the joint effort of several men and was intended to cover particularly the problems of war. It is a practical manual for the World War. Some of the problems have changed

until the care of the sick of a peace time army and the service to World War veterans have given to the radiologists of the Army precisely the same problems as confront their colleagues in civil life. The chapters treated are X-ray Physics, Dangers and Protection, Laboratory Experiments, Fluoroscopy, Technic, Field Unit, Localization, Bones and Joints, Sinuses, Mastoids and Brain, Teeth and Maxillae, Thoracic Viscera, Urinary Tract, and Gastrointestinal Tract. Therapy is not considered, but in a clear and concise form there is provided an adequate description and discussion of apparatus, technic, and interpretation. Practical suggestions for safeguarding the use of x-ray apparatus and for handling radioactive substances make a valuable section. The localization of missiles and other foreign bodies is treated very completely. The mechanical structure of this manual is pleasing and practical. In addition to its special use in military service, this book is admirably adapted to the needs of those whose situation is such that they are required to do occasional roentgenologic work without the elaborate equipment of laboratories devoted exclusively to this specialty. Is it not equally true of the roentgenologist outside of the Army that "he must remember, however, that his work is valuable only in so far as he assists the physician or surgeon in arriving at correct conclusions, and that this can be accomplished only by mutual cooperation?"

Pathology for Nurses By EUGENE C. PIERRE, MD, Pathologist and Director of the Clinical Laboratories of the West Suburban Hospital, Oak Park, Illinois, Consulting Pathologist, Chicago State Hospital. 251 pages, 65 illustrations, some in color. F. A. Davis Company, Philadelphia, 1932. Price, \$1 75.

As clearly stated in the preface, and as apparent from the text, this book is intended to provide instruction in the fundamentals of pathology, of necessity simply and briefly put, and to give detailed practical instructions for the intelligent handling of specimens required for the laboratory. In general the subject matter is fairly well chosen to meet these ends. A simply written intro-

ductory chapter explaining what is meant by normal and abnormal life, health and disease, would be of value. There are many statements in respect to detailed pathology which are open to question. Some may be the result of an unusual personal experience. It is not the experience of most pathologists, for instance, to find that "diaphragmatic hernia is not an uncommon developmental anomaly." Curiously, actinomycosis is said to be caused by a "yeast-like organism", and to be a condition "rarely occurring in this country." The chapter headings are extremely misleading, for leprosy and Hodgkin's disease are considered in the chapter headed Tuberculosis, and gonorrhea and chancroid under Syphilis. Illustrations of malignant melanoblastoma, both primary and secondary, occur in the chapter headed Benign Tumors. This book shows the results of careful proof reading and non-medical editorial supervision. The typography is excellent.

Modern General Anesthesia, A Practical Handbook By JAMES G. POE, M.D., Lecturer on General Anesthesia in the Medical and Dental Departments of Baylor University, Anesthesiologist of Baylor University Hospital of Dallas, Consulting Anesthetist to the Shriners' Hospital for Crippled Children, and Parkland Hospital, Dallas, Texas, etc. Second Edition, Completely Revised and Enlarged. 231 pages, 12 illustrations and 2 charts. F. A. Davis Company, Philadelphia, 1932. Price \$2.50.

In *Modern General Anesthesia* the author presents the subject matter in a very clear and concise manner which should make the book of great value to the student of anesthesia. At the beginning is a very complete chart (which should be redrawn for the next edition to eliminate the misspelled words) showing the zones of the third stage of ether or ether sequence anesthesia. At the end of each descriptive section is a brief, easily followed outline of the important material in the section. Throughout the book, Dr. Poe stresses important points some of which the untrained are likely to overlook. He also emphasizes the importance of standard colors for gas tanks to prevent confusion

and accidents, particularly in emergencies. The author believes that the danger of ignition during the administration of ethylene is practically the same as with ether and warns of the danger of static ignitions occurring when using ethylene or ether in fractional rebreathing since there is insufficient humidity from rebreathing to eliminate the possibility of static discharge. The same danger exists in giving ethylene intermittently for relief of labor pains. He feels that ethylene has a decided place in anesthesia. The author discusses intelligently the choice of an anesthetic and states that because of its strong likelihood of causing protoplasmic poisoning, chloroform should not be used as an anesthetic except in emergency. The nonvolatile anesthetics and local and spinal anesthesia are described in detail. "Since the advent of the use of the pleasant gaseous anesthetics, every patient should be induced into anesthetic sleep as comfortably as they go to sleep in their own bed at home, and a technic that does not admit of this accomplishment has no place in modern anesthetic practice." This quotation is characteristic of the attitude of the author toward his chosen field.

R C W

Counts and Doctors By LLOYD PAUL STRYKER. xvi + 236 pages. The Macmillan Co., New York, 1932. Price \$2.00.

"Taking a leaf from the pages of preventive medicine, I have tried to explain the nature of a malpractice action, in the hope that an understanding of this malady may render those who understand it more immune to its dread ravages." Thus does the author state the purpose of the work which he has so well accomplished. For many years the general counsel for the Medical Society of the State of New York he draws upon a rich practical experience for much of the material presented. Most of the treatises on the legal aspects of the practice of medicine neglect the phase of the subject emphasized here—that is those events and policies which bring the physician into court as defendant or expert witness in an action for malpractice. An extended discussion of I and II of the patient-physician relationship with the legal responsibilities of the physician

leads to the development in part III of the elements of the action for malpractice with a careful elucidation of the necessary proofs to be established by the plaintiff and the possible lines of defense which may be undertaken by the defendant. Of equal value is the explanation of the most common errors committed by physicians which expose them to malpractice suits. The simple straightforward advice herein contained can scarcely fail to be of value to those in all the branches of medicine. For those interested in the many cases quoted and cited as illustrative material, very complete and satisfactory indices are provided. This interesting and valuable book went to the fourth printing in five months. It deserves to be a medical "best seller". J C B

The Principal Nervous Pathways. Neurological Charts and Schemes with Explanatory Notes. By ANDREW THEODORE RASMUSSEN, Ph.D., Professor of Neurology, Department of Anatomy, University of Minnesota Medical School, Minneapolis,

Minn. 73 pages, 28 figures. The Macmillan Company, New York City, 1932.

As the outgrowth of an extensive teaching experience Rasmussen has prepared this monograph to aid the student in acquiring usable knowledge of the more important nervous pathways in the central nervous system. It represents a correlation and fusion of structural information (morphology) with knowledge of function, and thus it builds a dynamic conception of the nervous system. The structural diagrams are supplemented by schematic outlines embodying much of the same information. A certain element of dogmatic presentation is necessary to bridge the gaps in this field. This is inevitable, and such changes as may be made desirable by additions to our knowledge can be incorporated in the subsequent editions which are sure to be required for such a well-conceived book. While intended for the student, both undergraduate and more advanced, this should prove a valuable aid to the practitioner and a reference source not to be despised by even the professional neurologist.

College News Notes

POST-CLINICAL TOUR

Immediately following the completion of the San Francisco Clinical Session, about 125 members of the College and their families left on a Post-Convention Tour, visiting the Yosemite Valley, Los Angeles and environs, and the Grand Canyon of Arizona.

From Sunday morning, April 10, to Tuesday noon, April 12, the group were entertained in Los Angeles by members of Southern California, under the leadership of Dr Francis M Pottenger, the incoming President, and Dr Egerton L. Crispin, Governor for Southern California. Trips were arranged through Hollywood and Beverly Hills to the sea, with a visit to the beautiful Japanese home and gardens of Mr Bernheimer, overlooking Santa Monica Bay and

the Pacific Ocean. Dinner and a delightful program were given at the Uplifters' Club. Will Rogers was among the entertainers at the Club, and many members had the opportunity of meeting him personally and shaking his hand. A visit was also made to Pasadena and the California Institute of Technology where the Wind Tunnel of the Guggenheim School of Aeronautics and the Million Volt X-Ray Tube were demonstrated. Dr Pottenger acted as host to the entire group for luncheon on the lawns of the Pottenger Sanatorium in the foothills of the Sierra Madre Mountains in Monrovia. Members were also taken to the Huntington Library at San Marino, where they saw the Gutenberg Bible and the Huntington Galleries, where hang many rare and noted paintings, including the "Blue Boy." The Mission San Gabriel, one



PART OF THE POST-CLINICAL SESSION GROUP OF THE LAWSON GROUP
POTTENGER SANATORIUM, MONROVIA

of the oldest of the historic Spanish Missions of early California, was also visited

Never before has such a delightful Post-Convention Tour been arranged, and the appreciation of one and all was expressed to every member of the College in Southern California, who so graciously assisted in the arrangements of the program

WILLIAM D STROUD ELECTED TREASURER OF THE COLLEGE

Following the sudden and untimely death of Dr Elmer H Funk, who was elected Treasurer of the American College of Physicians during the San Francisco Session in April, the Board of Regents have elected Dr William D Stroud, of Philadelphia, Treasurer, with duties to start at once

Dr Stroud is Associate Professor of Cardiology in the University of Pennsylvania Graduate School of Medicine, Physician-in-Chief of the Heart Clinic, Pennsylvania Hospital, a member of the staff of the Robinette Foundation of the University of Pennsylvania, Physician-in-Charge of the Children's Heart Hospital, and Cardiologist to the Bryn Mawr Hospital

ARRANGEMENTS FOR MONTREAL SESSION, 1933

The Seventeenth Annual Clinical Session of the American College of Physicians will be held in Montreal, Canada, February 6-10, 1933. The Board of Regents of the College during the San Francisco Session, specified the month of February, in accordance with the original practice of the College to meet in midwinter when there would be no conflicts with the meetings of other national bodies or of state societies. The local Committee on Arrangements at Montreal, of which Dr Jonathan C Meakins is General Chairman, selected the week of February 6 as a time that would be most suitable to the local profession, a time when the weather would probably be most settled, a time at which the winter sports are at their height, and the week preceding the meeting of the Council on Medical Education at Chicago, at which a number of the members of the American College of Physi-

cians must go. The personnel of the Montreal Committees is as follows.

General Chairman

Jonathan C Meakins

Committee on Arrangements

J C Meakins, Chairman

C F Martin

E P Benoit

J E Dubé

R H M Hardisty

A T Henderson

Joseph Kaufmann

D S Lewis

E H. Mason

C F Moffatt

I M Rabinowitch

C G Sutherland

H P Wright

Committee on Clinics

J C Meakins, Chairman

C F Moffatt

I M Rabinowitch

E P Benoit

J E Dubé

H P Wright

E Dubé

Committee on Auditorium and Local Transportation

Joseph Kaufmann, Chairman

R H M Hardisty

E H Mason

Committee on Publicity

C G Sutherland } Joint

E P Benoit } Chairmen

(Additional appointments pending)

Committee on Convocation and Banquet

C F Martin } Joint

E de L Harwood } Chairmen

D S Lewis

J E Dubé

A T Henderson

Committee on Entertainment of Visiting Women

Mrs J C Meakins, Convenor

(Additional appointments pending)

President F M Pottenger appointed on May 3, 1932, the following Nominating Committee

James H Means, Boston, *Chairman*

Noble Wiley Jones, Portland

Ernest B Bradley, Lexington

Edward J G Beardsley, Philadelphia
Charles F Martin, Montreal

The above appointments are in accordance with the provision of the By-Laws, Article I, Section 3, which states that the President "shall appoint within one month after induction to office a Nominating Committee of five, composed of two members of the Board of Regents, two members of the Board of Governors, and one Fellow at large, whose duty it shall be to nominate candidates for the elective offices, Board of Regents, and Board of Governors. The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective States, Provinces or Districts which will be represented by the nominees, if elected. The list of nominees for President-Elect, and for the First, Second and Third Vice Presidents shall be submitted to all the Masters and Fellows of the College at least one month before the annual meeting, and the election of all nominees shall be by the members of the College at its annual business meeting. This does not preclude nominations made from the floor at the annual meeting itself."

Under the sponsorship of Dr A B Brower (Fellow), Dayton, Ohio, Governor of the College for the State of Ohio, a meeting and luncheon of all Ohio members of the College was held during the Ohio State Medical Association's meeting at Dayton during the first week in May. Those present decided to hold a similar meeting annually at the time of the annual meeting of the Ohio State Medical Association in the future. Among those who attended the luncheon were thirty-three Fellows and thirteen Associates.

Dr Adolph Sachs (Fellow), Omaha, Nebr., Governor of the College for the State of Nebraska, was elected President of the Nebraska State Medical Association at the annual meeting of that society during the week of May 23.

Dr Homer Davis (Fellow), Genoa, Nebr., was elected a Vice President.

Cecil O Lorio (Fellow), Baton Rouge, La., was the symposiarch and contributed a

paper on "Childhood Type Tuberculosis" in a symposium on tuberculosis by the Staff of Our Lady of the Lake Sanitarium, Baton Rouge, March 23, 1932. Dr Lester J Williams (Fellow), Baton Rouge, read a paper also, his subject being "X-ray of Tuberculosis."

During the five days following the San Francisco Clinical Session, Dr Linn J Boyd (Fellow), New York City, addressed the Sophomore, Junior, and Senior classes at the University of California, was the guest speaker at Dr Kerr's Staff Conference, and addressed the San Francisco County Medical Society.

Acknowledgement is made of the receipt of gifts to the College Library of publications by members, as follows:

Dr Frederick R Barnes (Fellow), Fall River, Mass.,—1 reprint,

Dr Grafton T Brown (Fellow), Washington, D C,—1 reprint,

Dr Lewis W Brown (Associate), Newark, N J,—1 reprint,

Dr I W Held (Fellow), New York, N Y,—10 reprints,

Dr Roland N Klemmer (Fellow) Lancaster, Pa,—2 reprints,

Dr Lowell L Lane (Associate), Philadelphia, Pa,—3 reprints,

Dr James Z Naurison (Fellow), Springfield, Mass,—1 reprint,

Dr Paul H Ringer (Fellow) Asheville N C,—4 reprints,

Dr Karl Rothschild (Fellow), New Brunswick, N J,—1 reprint,

Dr W E R Schottstaedt (Fellow), Fresno, Calif,—1 reprint,

Dr Leon L Solomon (Associate), Louisville, Ky,—2 reprints,

Dr Henry K Taylor (Fellow) New York, N Y,—1 reprint,

Dr Edwin Henes, Jr (Fellow) Milwaukee, Wis.—1 book "Minutes Proceedings of the Inter State Postgraduate Medical Association of North America for 1931".

Dr E A Baumgartner (Fellow), Clifton Springs, N Y—collected papers from the Clifton Springs Sanitarium and Clinic on "Studies in Tropical Sprue", bound in one volume,

Dr David W Kramer (Associate), Philadelphia, Pa—4 reprints,

Dr George B Lake (Associate), Highland Park, Ill—1 reprint,

Dr C Ray Lounsberry (Fellow), San Diego, Calif—1 reprint,

Dr V C Rowland (Fellow), Cleveland, Ohio—3 reprints,

Dr A Comingo Griffith (Fellow), Kansas City, Mo—2 books formerly the property of his father, Dr Jefferson D Griffith "A Compleat Treatise of the Gravel and Stone" by Nicholas Robinson, M D, 1723,

"A Treatise on Surgical Anatomy" by Velpeau (in two volumes), 1830

Dr Samuel H Snider (Fellow), Kansas City, Missouri, addressed the Hennepin County, Minnesota Medical Society on March 16 on "Routine Methods in the Diagnosis of Pulmonary Tuberculosis" He also addressed the Minnesota Trudeau Society that evening on the subject of "Bronchial Function in Pulmonary Tuberculosis"

Dr Grafton Tyler Brown (Fellow), Washington, D C, addressed the Atlantic County Medical Society, Atlantic City, N J, on March 11 His subject was "Seasonal Hay-Fever", with special reference to the Middle Atlantic States Dr. Samuel Barbach (Fellow) and Dr Samuel L Salasin (Fellow), both of Atlantic City, participated in the discussion

Articles by Dr Brown also appeared in the January, 1932, issue of the Journal of Allergy and in the February issue of Archives of Otolaryngology

Dr Harlow Brooks (Fellow), New York, N Y, was elected President and Dr L T LeWald (Fellow), New York, N Y, was elected Treasurer of the International Medical Club of America, at the Annual Meeting, April 1, 1932

The following is the title of an article published by Dr. Brown in the Journal of Allergy

by the Hudson County Tuberculosis Hospital and Sanatorium, its staff and friends, "in recognition of the achievements and devotion to the welfare of society engendered by Dr Berthold S Pollak" (Fellow), on the occasion of the Twenty-fifth Anniversary of his medical directorship of that institution

Dr Warren Pearce (Fellow), Quincy, Ill, delivered the Chairman's address before the Medical Section of the Illinois State Medical Society meeting at Springfield, May 17-19, 1932

Dr Andrew C Ivy (Fellow), Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago, delivered the annual address before the Gorgas Medical Society of the School of Medicine, University of Alabama, May 7 His subject was "Physiologic Aspects of the Etiology, Symptoms, and Treatment of Gastroduodenal Ulcer".

Dr Edward E Cornwell (Fellow), Brooklyn, N Y, read a paper before the American Therapeutic Society at Baltimore, May 17, on "A Problem of the Circulation"

Dr David Riesman (Fellow), Philadelphia, Pa, delivered an address on "Vascular Crises" before the Evanston Branch of the Chicago Medical Society, April 7, 1932.

Dr Arthur A Shawkey (Fellow), Charleston, W Va, addressed the Hempstead Academy of Medicine, Portsmouth, Ohio, on the evening of April 11, 1932 His subject was "The Hypertonic Infant"

Dr Samuel M Feinberg (Fellow), Chicago, Ill, spoke before the Kankakee County Medical Society (Illinois), April 14, 1932, his subject being "Allergy of the Respiratory Tract".

Dr Peter Whitman Rowland (Fellow), University, Miss, at a recent meeting of the State Medical Association (Jackson, Miss, April 12) announced his forty-ninth year of continuous membership in the Association.

Dr Samuel A Levine (Fellow), Boston, Mass., delivered an address and conducted clinics on various aspects of heart disease before the Orleans Parish Medical Society at New Orleans on March 31, 1932

Dr Edward J Stieglitz (Fellow), Chicago, Ill., addressed the Saint Joseph Clinical Society (St Joseph, Mo) April 21, 1932, on "Nephritis in Pregnancy", and again, at a noon luncheon, on "The Etiology and Pathogenesis of Hypertension"

Dr Robert L Schaefer (Fellow), New York, N Y, gave a talk before the Noon Day Study Club of Detroit on "Endocrine Diagnosis and Treatment", and spoke before the staff of Grace Hospital of Detroit on "The Anterior Lobe of the Pituitary", on April 15, 1932

Dr Udo J Wile (Fellow), Ann Arbor, Mich., addressed the Fifty-ninth Annual Meeting of the Northern Tri-state Medical Association at Toledo, Ohio, on April 12, 1932 His subject was "The Fluid Status of Syphilis Therapy" Dr Wile also gave a dermatological clinic

Dr Warren T Vaughan (Fellow), Richmond, Va, spoke before the Association on "The Control of Pollen Allergy"

Dr William C Voorsanger (Fellow), San Francisco, Calif, was recently elected President of the California State Tuberculosis Association

Dr Arthur C Christie (Fellow), Washington, D C, President, Medical Society of the District of Columbia, has been selected as chairman of the executive committee in charge of the annual early diagnosis campaign of the Association for the Prevention of Tuberculosis, which was launched in the District the first part of April In a talk reviewing the history of "Tuberculosis Reporting", Dr Christie appealed for more effective reporting of cases

The annual session of the Medical Society of the District of Columbia was held, May 4-5, 1932, under the presidency of Dr Christie.

Dr Lawrason Brown (Fellow), Saranac Lake, N Y, delivered the Hermann M Biggs Memorial Lecture at the New York Academy of Medicine on May 5, 1932 His subject was "Robert Koch and His Life Work" The Biggs lecture was established in 1925 by the widow of Dr Biggs

Dr William D Anderson (Fellow), Chattanooga, Tenn, was elected a vice president of the Tennessee State Medical Association at its annual meeting in Memphis on April 14, 1932

Dr Daniel J Glomset (Fellow), Des Moines, Iowa, was made president-elect of Medical Society of the Missouri Valley at its annual meeting in Omaha, March 29-31, 1932

Dr Alfred Henry (Associate), Indianapolis, Ind, president, National Tuberculosis Association, addressed the Illinois Tuberculosis Association at its annual meeting in Danville, Ill, on April 25, 1932 He spoke on "Our Job Now"

Dr John A Lanford (Fellow), New Orleans, La, has been made chairman of a state cancer committee organized, February 22, by Dr Sidney C Barrow in cooperation with the American Society for the Control of Cancer

Dr Lewellys F Barker (Fellow) Baltimore, Md, Professor Emeritus of Medicine Johns Hopkins University School of Medicine, delivered the annual Alpha Omega Alpha lecture at Jefferson Medical College Philadelphia Pa, on March 4, 1932 His subject was "Medical and Other Conditions in Soviet Russia"

Dr Louis Hamman (Fellow) Baltimore Md, presided over the forty-fourth annual meeting of the American Climatological and Clinical Association, held at the Seaside Golf Club, Absecon N J near Atlantic City May 5-7 Among the speakers at the scientific sessions were the following fellows: Dr George R. M. : Philadelphia, Pa; Dr J Burne Anderson Jr, New York, N Y; Dr Paul D White, Philadelphia, Pa.

Dr Joseph H Pratt (Fellow), Boston, Mass, was chairman of the roundtable discussion on diseases of the heart and Dr Lawrason Brown (Fellow), Saranac Lake, N Y was chairman of the roundtable discussion on diseases of the lungs

At the Thirty-Third Annual Meeting of the American Therapeutic Society, held in Baltimore, Maryland, on May 16 and 17, the following officers were elected for the coming year

President, Frank Smithies (Master), Chicago, Ill ,

1st Vice-President, Julius Friedenwald (Fellow), Baltimore, Md ,

2nd Vice-President, Alpheus F Jennings (Fellow), Detroit, Mich ,

3rd Vice-President, Grafton Tyler Brown (Fellow), Washington, D C ,

Secretary, Oscar B Hunter (Fellow), Washington, D C ,

Treasurer, Alphonse McMahon (Fellow), St Louis, Mo

Dr Hugh S Cumming (Fellow), Washington, D C, early in March took the oath of office as Surgeon-General of the U S Public Health Service for the fourth time. Dr Cumming entered the Service thirty-eight years ago and has been Surgeon-General since 1920

The American Association of the History of Medicine held its annual meeting in Atlantic City, May 2, 1932, with Dr David Riesman (Fellow), Philadelphia, presiding. The following Fellows contributed to the program: Dr Carl V Weller, Ann Arbor, Mich; Dr Charles W Burr, Philadelphia, Pa; Dr William S Middleton, Madison, Wis; Dr H R M Landis, Philadelphia, Pa; Dr Leodis F Barker, Baltimore, Md

Dr Harold Swank (Fellow), Quincy, Ill, is the author of an article "The X-Ray Diagnosis of Chronic Appendicitis," which appeared in the April 1932 issue of the *Quincy Medical Bulletin*

The following is a list of the members of the American Association of the History of Medicine who attended the meeting in Atlantic City, May 2, 1932

treatment of heart disease in Philadelphia, May 16-19, inclusive. The following Philadelphia members of the College participated as shown

Dr Ross V Patterson (Fellow), dean, Jefferson Medical College,—“A Rational Plan for the Diagnosis and Treatment of Heart Affections”

Dr Edward J G Beardsley (Fellow), clinical professor of medicine, Jefferson Medical College,—“Problems Associated with Aortic Regurgitation”

Dr Elmer H Funk (Fellow), professor of materia medica, therapeutics, and clinical medicine, Jefferson Medical College,—“Acute Endocarditis”

Dr Henry K Mohler (Fellow), assistant professor of medicine, Jefferson Medical College,—“Heart Block”

Dr Edward Weiss (Fellow), associate in medicine, Jefferson Medical College,—“Congenital Heart Disease”

Dr William Egbert Robertson (Fellow), professor of theory and practice of medicine, Temple University Medical School,—“The Diagnosis of the Failing Heart Muscle”

Dr H Brooker Mills (Fellow), professor of pediatrics, Temple University Medical School, (and associates),—“Heart Disease in Children”

Dr Joseph B Wolffe (Associate), associate professor of cardiovascular diseases, Temple University Medical School,—“Coarctation of the Aorta” (with case demonstration)

Dr E B Krumbhaar (Fellow), professor of pathology, U of P Medical School,—“Demonstration of the Pathology of the Cardiovascular System”

Dr John Eiman (Fellow), pathologist, Presbyterian Hospital,—“Anatomy of the Conducting System with Demonstration of Injection of the Purkinje System and Demonstration of Injection of Coronary System”

Dr William D Stroud (Fellow), professor in cardiology, Graduate School of Medicine, U of P,—“Treatment of Cardiac Arrhythmia”

Dr James E Talley (Fellow), emeritus professor of cardiology, Graduate School

of Medicine, U of P,—“Cardiovascular Phenomena of Thyroid Disease”

Dr S Calvin Smith (Fellow), associate professor of cardiology, U of P,—“Demonstration and Discussion of Electrocardiography in Diagnosis and Treatment of Heart Disease”

Dr Charles C Wolferth (Fellow), Robinette Foundation, U of P,—“The Relation of Cardiology to General Medicine”

Dr David Riesman (Fellow), professor of clinical medicine, U of P Medical School,—“Some of the Difficulties in the Diagnosis of Mitral Stenosis”

Dr Truman Schnabel (Fellow), physician of the Philadelphia General Hospital and assistant in medicine, U of P Medical School,—“Diet and the Gastro-intestinal Tract in Relationship to Cardiovascular Disease”

Dr William H Kraemer (Fellow), Wilmington, Del, was elected president of the Alumni Association of Jefferson Medical College at the thirty-sixth annual meeting of the association, February 18

The following Fellows were also elected to office

Dr Ross V Patterson,—vice chairman,

Dr Louis H Clerf,—vice president,

Dr Harold W Jones,—treasurer

Dr Edward J G Beardsley (Fellow), Philadelphia, Pa, Governor for Eastern Pennsylvania, addressed the Bridgeport, Connecticut, Medical Association on “Practical Post-Graduate Instruction in our own offices”, May 3, 1932

Dr Daniel P Griffin (Fellow), Bridgeport, Conn, is President of the Association and at his request Dr Beardsley also spoke briefly on the objects and ideals of the American College of Physicians

Dr Hyman I Goldstein (Associate), Camden, N J, recently read a paper before the Medical Society of New Jersey, at Atlantic City, on the subject “Recent Advances in the Treatment of Some Diseases in Children”

Dr Pauline Williams (Fellow), Richmond, Va, national president of the Alpha

Epsilon Iota Fraternity of medical women, presided at the biennial convention of that organization held at Portland, Ore. June 10-12, inclusive. This fraternity embraces a membership of 1,500 women physicians and women medical students, the chapters are established in twenty-two class A medical schools throughout the country

Dr Allen K Krause (Fellow), Tucson Ariz, delivered the Theodore B Sachs resident lectures in tuberculosis at the University of Illinois College of Medicine, April 18-29. This lectureship is endowed by the Chicago Tuberculosis Institute

Dr John H Peck (Fellow), Des Moines, Iowa, was re-elected President of the Iowa Tuberculosis Association at its recent annual meeting in Burlington

Dr J A Myers (Fellow), Minneapolis, Minn, addressed the Fifth Councilor District Medical Society at Boone, Iowa, April 13, on “Tuberculosis in Childhood”

The following Fellows of the College participated on the program at the sixty-fifth annual session of the Mississippi State Medical Association, April 12-14, at Jackson Miss, as indicated

Dr Lloyd Thompson, Hot Springs, Ark — “Modern Renaissance of Syphilis”

Dr Allan C Eustis, New Orleans, La — “Headaches Causes and Treatment”

Dr James G Carr, Chicago, Ill — “Treatment of Cardiac and Renal Edema”

Dr Edward C Mitchell, Memphis, Tenn — “Asthma from the Viewpoint of the Pediatrician”

Dr Waller S Leathers, Nashville, Tenn presented the annual oration

Dr Henry A Christian (Fellow), Boston, Mass, addressed the Mahoning County Medical Society, Youngstown, Ohio, on April 2, its sixth annual Postgraduate Dinner, on “Varieties of Bright's Disease and their Management and Direct and Indirect Uses”

Dr Samuel A Levine (Fellow), Boston, Mass, also addressed the same society on “A Clinical Comparison of Heart Disease”

and "Bedside Recognition and Treatment of Cardiac Irregularities"

Dr Ernest R Zemp (Fellow), Knoxville, Tenn, spoke on "Gastric Ulcer" before the ninety-ninth annual meeting of the Tennessee State Medical Association at Memphis, April 12-14

At a meeting in the Embassy of Mexico, Washington, D C, on April 5, Surgeon General Hugh S Cumming (Fellow) was appointed President of a newly organized chapter of the Pan-American Medical Association for the District of Columbia

Dr Samuel A Brown (Fellow), New York, N Y, recently resigned as Dean of New York University and Bellevue Hospital Medical College, and has been made a member of the University Council Dr Brown had been Dean for sixteen years

Dr Henry J Ullmann (Fellow), Santa Barbara, Calif, addressed the San Diego County Medical Society, May 5, on "The Work of the Cancer Commission"

Dr Walter C Alvarez (Fellow), Rochester, Minn, was one of the guest speakers at the eighty-third annual session of the Medical Association of Georgia, May 17-20, at Savannah Dr Alvarez's subject was "Practical Points in the Care of Patients with Indigestion"

Dr James H Hutton (Associate), Chicago, Ill, has been appointed Consulting Endocrinologist to the hospitals of the Illinois State Department of Public Welfare

The following Fellows of the College addressed the Medical and Surgical Faculty at the Medical Society's recent meeting in Baltimore, April 23-27

Dr Henry A Carter, Boston, Mass.—"The Pathology of the Therapy of Tuberculosis"

Dr L B McBrayer, Southern Pines, N C.—"Studies in the Pathology of the Heart and the Lungs"

"Relation of the State Board of Health to the General Practitioner".

In connection with a special four months' course in Internal Medicine held at the Harvard University Medical School, April 1 to August 1, Dr Frank Dennette Adams (Fellow), Boston, Mass, has charge, for six weeks, of a course in Internal Medicine at the Massachusetts General Hospital, which began June 20 During July, Dr. Samuel A Levine (Fellow), Boston, Mass, will conduct a course in modern diagnosis and treatment of heart disease at the Peter Bent Brigham Hospital

The following members of the College contributed to the program of the Nebraska State Medical Association, held at Lincoln, Nebr, May 24-26

Dr Ernest S Wegner (Associate), Lincoln, Nebr—"Infant Feeding",

Dr Arthur D Dunn (Fellow), Omaha, Nebr—"Cholecystography",

Dr Andrew C Ivy (Fellow), Chicago, Ill—"Physiology of Mucus Secretion with some experimental results on the prevention of Ulcer with 'Gastric Mucin'",

Dr Walter C Alvarez (Fellow), Rochester, Minn—"Practical Points in the Handling of Patients with Gastro-Intestinal Disease"

Dr. Edgar B Friedenwald (Fellow), Baltimore, Md, on May 13 addressed the Atlantic County Medical Society, Atlantic City, N J, on "Diet Problems and Therapeutics in Children"

Dr L B McBrayer (Fellow), Southern Pines, N C, was re-elected Secretary of the Medical Society of the State of North Carolina at its annual meeting on April 20

The following Fellows of the College delivered papers at the annual meeting of the National Tuberculosis Association held at Colorado Springs, June 6-9

Dr James Burns Amberson, Jr, New York, N Y—"Comparative Value of Paper and Celluloid Films for Chest Roentgenograms, Report on 1,000 Cases",

Dr Carl H Greene, Rochester, Minn—

"Treatment of Addison's Disease with Cortical Hormone of the Suprarenal Gland"

Dr Gerald B Webb (Fellow), Colorado Springs, Colo, addressed the annual dinner meeting on "Robert Koch".

Dr Roy Lyman Sexton (Associate), Washington, D C, addressed the Tippecanoe County Medical Society, May 5, at Lafayette, Ind, on "Colon Disturbances and Involvements including Endocrine Aspects"

Dr William S Middleton (Fellow), Madison, Wis, and Dr Arthur L Anderson (Fellow), Springfield, Mo, addressed the Missouri State Medical Association at Jefferson City, May 23-26, on "Syphilis of the Circulatory System" and "Value of Routine Basal Metabolism in the Examination of Patients", respectively.

Dr Louis E Viko (Fellow) was recently appointed Health Officer of Salt Lake City

Dr George G Ornstein (Fellow), New York, N Y, spoke before the Cambria County Medical Society, Cresson, Pa, May 12, on "Diagnosis and Treatment of Pulmonary Tuberculosis"

Dr Willis F Manges (Fellow), Philadelphia, Pa, delivered an address on "Relation of Sinus Infection to Pulmonary Diseases" before the Eleventh Councilor District Medical Society, May 19

"Collapse Therapy in the Treatment of Pulmonary Tuberculosis" was the subject of a paper delivered by Dr Charles H Marcy (Fellow), Pittsburgh, Pa, before the Erie County Medical Society, Erie, Pa, on May 3

Dr. Joseph H Barach (Fellow), Pittsburgh, Pa, addressed the Crawford County Medical Society, May 9, on "Focal Infection"

Dr James H Means (Fellow), Boston, Mass, was re-elected Secretary of the As-

sociation of American Physicians at its recent meeting

At the annual meeting of the American Gastro-Enterological Association, May 2, Dr Charles G Lucas (Fellow), Louisville, Ky, was reelected Secretary

Dr Arthur L Bloomfield (Fellow), San Francisco, Calif, was elected President of the American Society for Clinical Investigation, on May 2

Dr Howard T Karsner (Fellow), Cleveland, Ohio, was recently reelected Secretary of the American Association of Pathologists and Bacteriologists for the ensuing year

Dr William E Engelbach (Fellow), New York, N Y, addressed the staff of St John's Hospital, Brooklyn, May 3, on "Results of Therapy in Pituitary Disorders" On May 16, Dr Engelbach addressed the joint meeting of the Baltimore Medical Society and the American Therapeutic Society at Baltimore on "Endocrine Therapy in Disorders of the Hypophysis"

Dr Abraham M Ornstein (Fellow), Philadelphia, Pa, has been appointed Assistant Professor of Neurology in the University of Pennsylvania School of Medicine. Dr Ornstein has also been elected President of the Philadelphia Neurological Society

Dr John G Fitzgerald (Fellow), Toronto, Ont, has been appointed Dean of the University of Toronto Faculty of Medicine

Dr E J G Beardsley (Fellow) Philadelphia, Pa, as a guest speaker, addressed the Kiwanis Club of Woodbury, N J, May 12, on "The Influence of the Hospital on the Community"

Dr Ralph K Hollnbeck (Fellow), Westville, N J was also a guest of the Club on this occasion

Dr Walter M Soper (Fellow) Princeton, Ohio was elected President of the American Society of Clinical Pathology at its recent meeting at New Orleans

Dr David W Kramer (Associate), Philadelphia, Pa, was recently appointed Visiting Physician to the Medical Staff at the St Luke's and Children's Hospitals

PERPETUAL MEMORIAL FUND
IN HONOR OF

DR JOHN B DEAVER

The Aid Association of the Philadelphia County Medical Society is establishing a special perpetual fund in honor of Dr John

B Deaver, only the income of which will be used to afford aid to needy physicians and their families. All friends of Dr Deaver are invited to participate. All money received will be placed in the Dr John B Deaver Perpetual Memorial Fund. Checks should be drawn to the order of the Aid Association of the Philadelphia County Medical Society and sent to

Dr Francis Heed Adler, Secretary,
313 So 17th Street, Philadelphia, Pa

OBITUARIES

DR ORLANDO HENDERSON PETTY

Dr Orlando Henderson Petty (Fellow), Philadelphia, Pennsylvania, an outstanding medical hero of the World War, died as the result of a self-inflicted gunshot wound, at his home on June 2, 1932. Dr Petty was born in Cadix, Ohio, in 1874, and received his academic education in that State, with his B S degree from Franklin College. He was graduated in medicine from the Jefferson Medical College of Philadelphia in 1904. Dr Petty served his internship at St Timothy's Hospital, Roxborough, Philadelphia, in which institution he later became pathologist and visiting physician.

Shortly after Dr Petty completed his internship, a latent lung lesion made itself evident and he was advised to live an open-air existence with restrictions as to physical activities. Following the enforced and unwelcome vacation, an opportunity presented itself to become associated with Dr John B Lowman, a distinguished surgeon of Johnstown, Pa., in the field of industrial surgery. After a year spent in the west Dr Petty returned to the city of Philadelphia and soon later to a large general practice in

Roxborough where he became intimately associated with that great physician and medical teacher, Milton H Fussell. During this period Dr Petty became actively engaged in clinical teaching at the Jefferson Medical College, in which unremunerative and disinterested labor he continued for many years.

Dr Petty was, for a period, pathologist to the Germantown Hospital and faithfully served the City of Philadelphia as a medical inspector of its public schools.

At the time the United States entered the World War Dr Petty, in spite of excellent reasons why he should delay his military service, applied for active service and was immediately assigned to the Marine Corps. He sailed for France in August, 1917, and was soon serving in the field with the Fifth Marines, Second Division. The Corps to which Dr Petty was assigned was soon in the thick of battle and Dr Petty distinguished himself by outstanding bravery and heroism. For his conduct on the field of battle and his efficient professional services, he received the Congressional Medal of Honor, The United States Distinguished Service Cross, the Croix de Guerre

of France with palm, and the War Cross of Italy Dr Petty shared with Dr Joel T Boone the signal honor of being the only two officers of the Medical Corps to receive the Congressional Medal of Honor

Dr Petty was severely gassed during his heroic work with the wounded and spent much time in the Military Hospital as a result At the conclusion of the war Dr Petty returned to his home city a nationally acknowledged hero, but in extremely poor physical and financial condition, to take up the problems of readjustment

Without thought of self, Dr Petty began immediately and with characteristic energy and enthusiasm his undergraduate teaching and, at the same time, expended strength, that his disordered body could ill afford, in many medical, military service and other civic undertakings He was elected President of the Philadelphia County Medical Society, President of the Medical Club of Philadelphia, Commander of the Thomas Roberts Reath Post No 186 of the American Legion, National Commander of the Army and Navy Legion of Valor, and was active and interested in many similar agencies

In 1923, Dr Petty, whose medical interests had been especially with the disorders of metabolism, was elected Professor of the Diseases of Metabolism in the Graduate School of Medicine of the University of Pennsylvania where he came in contact with many graduate physicians from various parts of the world Medical articles and books from Dr Petty's pen and addresses by him stimulated a new interest in disorders of nutrition Dr Petty built at the Philadelphia General

Hospital a Department of Nutrition and headed an active service for the investigation of metabolic disorders

For a short period in 1931 Dr Petty served as Director of Public Health of Philadelphia to succeed the late Dr Andrew A Cairns, under whom Dr Petty had worked many years as Medical School Inspector

When one contemplates what Dr Orlando Henderson Petty accomplished in the twenty-eight years that he lived after receiving his medical degree and considers the handicap of persistent ill health that had never been absent, one can but wonder at the spirit, the determination and the unconquerable ambition that drove him on For many years prior to his military service, Dr Petty's life was a continual struggle to overcome a more or less active tuberculous lesion which he would never, consciously acknowledge Following the exposures and the physical and emotional stress of military life, the lung lesion became active and duodenal ulcer also developed which later was never entirely symptom free During the last months of Dr Petty's life a prostatic lesion developed that demanded surgical attention in spite of the existing serious contra-indications Although all this were not enough for one pain-racked and harassed brave man to endure, nature further restricted Dr Petty's activities by a serious painful and disabling attack of coronary occlusion Under the best conditions a physician in Dr Petty's precarious state of physical and mental health could only find a way out by taking a prolonged rest with entire freedom from physical and emotional stress and strain Dr Petty was fortunate

pressing period of our national history and the weight of all his ills and anxieties proved too great a strain. Throughout the United States are physicians whom Dr Petty has taught, with whom he has served, or with whom he has maintained friendly contacts. All these and many other admirers and friends will sincerely regret his passing. Dr Petty was a sincere, dogmatic, and conscientious teacher, perhaps, even in his end, there is a potential lesson for each of us to remember. A physician's health is his greatest asset and this, in spite of everything, he must preserve by a judicious care for his own body.

E. J. G. BEARDSLEY, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania).

DR JOHN ALDEN LICHTY

Dr John Alden Lichty was born in 1866. He received the degrees of Ph.B., Ph.M., and Ph.D. from Mount Union College, and M.D. from the University of Pennsylvania School of Medicine in 1893. He also did postgraduate work at the University of Pennsylvania in pathology and diseases of the digestive system; also postgraduate work at the University of Berlin. He was associate professor of medicine, University of Pittsburgh School of Medicine from 1909 to 1923; visiting physician, Mercy Hospital, Pittsburgh, 1912 to 1923; visiting physician, Columbia Hospital, Pittsburgh, 1906 to 1923; consulting physician, Presbyterian Hospital, Pittsburgh, 1916; superintendent, Children's Sanatorium and Clinic, 1923 to the time of his death. He was

a member and ex-president, Ontario County Medical Society; member and ex-chairman of Medical Section, New York State Medical Society, member and ex-vice chairman of Medical Section, American Medical Association; ex-member and ex-chairman of Medical Section, Pennsylvania State Medical Society, member and ex-president, American Gastro-Enterological Association; member American Climatological and Clinical Association, and member American Association for Advancement of Science. Dr Lichty was also a member of the Alpha Tau Omega and Phi Beta Pi fraternities. Dr Lichty was the author of many articles published in various medical journals and was the author of the chapter on Arthritis of the Text, "Diseases of Middle Life", F. A. Davis Company, also of the chapter on Appendicitis of Tice's "Practice of Medicine".

Dr Lichty was elected a Fellow of the American College of Physicians on December 29, 1916, and, therefore, was one of the earliest members of the organization. He served in a great many capacities in the College, including, member of the Board of Regents, 1922 to 1930, Third Vice-President, 1930 to 1932. One of his greatest contributions to the College was the early organization and Chairmanship of the Credentials Committee, on which he served faithfully and painstakingly for several years. The College was very near to Dr Lichty and even after the onset of his last illness he tried to serve the College and to attend one of its annual meetings.

DR CHARLES ROLLIN GRANDY

Charles Rollin Grandy (Associate), Norfolk, Va, died, June 10, 1932, from a cerebral hemorrhage and heart disease, aged 61 years

Dr Grandy was born in Norfolk, educated at the Norfolk Academy and the Bellevue High School. He held the degrees of A B and M D from the University of Virginia, the latter having been conferred in 1892. He did post-graduate work at the University of Berlin and the University of Freiburg, Germany. He was formerly attending physician to the Norfolk Protestant Hospital and physician-in-charge of the Norfolk Tuberculosis Clinic. For many years, he was chairman of the Norfolk School Board.

Early in Dr Grandy's career, he became interested in combating tuberculosis, to which work he devoted his energy the greater part of his life. He was responsible for the first comprehensive public health law in the State of Virginia. He organized the Anti-Tuberculosis League of Norfolk, and was its first president. He served in this capacity for twenty-seven years. In recognition of his service, Norfolk dedicated its tuberculosis sanatorium last November as the Charles R Grandy Sanatorium.

Dr Grandy was an ex-president of the Norfolk County Medical Society, a member of the Seaboard Medical Association, an ex-president of the Medical Society of Virginia, a Fellow of the American Medical Association, a member of the American Association for the Advancement of Science, a member of the American Public Health As-

sociation, a member of the National Tuberculosis Association, and had been an Associate of the American College of Physicians almost from its inception.

DR NELSON GAPEN

Dr Nelson Gapen (Fellow), Washington, D C, died January 7, 1932, of mastoiditis and meningitis, aged, 53 years.

Dr Gapen was born in Washington, where he attended public school and graduated from the Georgetown University School of Medicine in 1900. He served his internship in the Garfield Memorial Hospital of Washington, and pursued various post-graduate courses thereafter at the Army Medical School, Harvard Medical School, and the University of Michigan Medical School. For a time, he was Director of the Mary Imogene Bassett Hospital, of Cooperstown, New York. During the World War, he was in the office of the Chief Surgeon, Air Service U S A, assisted in the formation of the original Medical Research Board for Aviation, and attained the rank of Colonel. At the time of his death he was Professor of Materia Medica, Pharmacology and Therapeutics in the Georgetown University School of Medicine. Dr Gapen was a member of the Medical Society of the District of Columbia, the Association of Military Surgeons, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1929.

(Furnished through the courtesy of EUGENE R WHITMORE, M D, F A C P, Washington, D C.)

DR GEORGE HENRY
SHERMAN

Dr George Henry Sherman (Associate), Detroit, Michigan, died April 19, 1932, following an operation for appendicitis, in a hospital at Melbourne, Fla., aged 74 years

Dr Sherman was a graduate of the Chicago Medical College, 1883, he had not been in practice for several years.

DR ALEXANDER BROWN
KALBAUGH

Dr Alexander Brown Kalbaugh (Associate), Westernport, Maryland, died suddenly May 15, 1932, of coronary embolism, aged 48 years

Dr Kalbaugh was a graduate of the University College of Medicine, Richmond, Va., 1907, he did postgraduate work at the University of Liverpool during 1919. During the World War he served as First Lieutenant in the Medical Corps of the Air Service at Le Bourget and Orley Air Fields, France; he also served with Charge de Assault, French Tank Corps.

Dr Kalbaugh was an ex-president of the Allegany-Garrett County Medical

Society, an ex-vice president of the Tri-State Medical Society, member of the Medical and Chirurgical Faculty of Maryland, member of the Southern Medical Association, a Fellow of the American Medical Association and had been an Associate of the American College of Physicians since 1921.

DR ARTHUR J BURRIDGE

Dr. Arthur J. Burrige (Fellow), Winnipeg, Manitoba, Canada, died March 15, 1932, aged 56 years.

Dr Burrige was born in London, Ontario, Canada; attended the public and high schools of Winnipeg, and the Manitoba Medical College, from which he graduated in 1897. For many years he was Internist to the Grace Maternity Hospital and a member of the honorary attending staff of the Winnipeg General Hospital; he was Associate Professor of Medicine on the University of Manitoba Faculty of Medicine.

Dr Burrige was a member of the Winnipeg Medical Society, the Manitoba Medical Association, and had been a Fellow of the American College of Physicians since January 30, 1920

The Relation of Lipoid Nephrosis to Nephritis*†

By E. T. BELL, M.D., Minneapolis, Minn

"NEPHROSIS" is now generally used in a broad sense to include all forms of renal disease which are regarded as degenerative in nature, in contradistinction to "nephritis" which refers to those of inflammatory origin. However, in recent clinical literature many writers use nephrosis in a restricted sense to designate "lipoid nephrosis" only.

For many years, two forms of glomerulonephritis have been recognized.

a The *azotemic type* is characterized in the advanced stage by nitrogen retention. Edema is present from time to time but is not a conspicuous feature except in the acute stage and during acute exacerbations. Hypertension is nearly always present in the chronic stage, but is often absent in mild acute cases. The degree of albuminuria varies at different times, but is generally greater during acute phases. An increased number of erythrocytes is commonly found in the urine, especially during acute stages. Fatal cases terminate in uremia, and the postmortem reveals small contracted kidneys in the chronic form. There is a definite inflammatory reaction which leads to

occlusion of the glomerular capillaries. In subacute and chronic forms, the impermeable glomeruli gradually become hyaline and their associated tubules undergo atrophy.

b The *hydropic or nephrotic type* is characterized by marked edema and severe albuminuria. Death is frequently due to intercurrent infections and not to uremia. At postmortem large fatty kidneys are found. This form of renal disease, formerly named chronic parenchymatous nephritis, is now called "lipoid nephrosis." A great many investigators believe that lipoid nephrosis may be separated into two distinct types, viz., pure lipoid nephrosis, and a mixed type.

(1) Pure lipoid nephrosis. By general agreement the outstanding clinical features of this disease are the presence of marked albuminuria and severe edema, and absence of hypertension, hematuria, and renal insufficiency. Lipemia and decrease of plasma proteins, especially of plasma albumin, are also considered essential parts of the clinical picture. The anatomical definition demands enlarged kidneys with normal glomeruli and tubules filled with lipid droplets. It is considered a degenerative disease of the tubules.

(2) The mixed type. This form was called "nephritis with a large

*From the Department of Pathology, University of Minnesota, Minneapolis, Minn.

†Presented at the San Francisco Meeting of the American College of Physicians, April 4, 1932.

tendency" by Volhard and Fahr. It is also called the nephrotic type of glomerulonephritis. The disease has all the positive features of pure lipoid nephrosis but not all of its negative characteristics. Hypertension, hematuria, or impaired renal function are demonstrable in addition to the nephrotic syndrome. There are sharp differences of opinion as to the nature of this renal disease. Many writers consider it glomerulonephritis with superimposed nephrosis, or vice versa, others regard it as a form of nephrosis, and a few believe it to be a form of glomerulonephritis. The structural changes in the kidneys have not been extensively investigated. In a limited material I found non-contracted kidneys with fatty tubules, and a definite glomerular lesion. The glomerular lesion consists chiefly of thickening of the capillary basement membrane with narrowing of the capillary lumens, but there is a variable amount of endothelial proliferation.

A number of investigators attempt to make a sharp distinction between pure lipoid nephrosis and the mixed type. Some rigidly exclude from the "pure" group every case in which there is at any time during the course of the disease an elevation of blood pressure, an abnormal number of erythrocytes in the urine, or any impairment of renal function. If the onset follows an acute infection it is considered a mixed type. Other writers are more liberal and add to the group of pure nephroses cases that show minor deviations such as hypertension, a slight impairment of function, or a slight excretion of erythrocytes in the urine.

In the few published re-

ports which conform to the rigid definition as outlined above. The more thoroughly the patient is studied, the more frequently some minor deviation is demonstrated; yet there are a few cases which conform to the rigid definition. It is obviously inconsistent to exclude thoroughly studied cases which show minor deviations, and to include cases with incomplete data that show nothing inconsistent with pure nephrosis. In his recent review, Leiter, 1931, seems to accept as pure nephrosis cases without complete clinical study when the pathological report stated that the glomeruli were normal.

THE CLINICAL PHENOMENA OF LIP- OID NEPHROSIS

Age Incidence. According to the published reports, lipoid nephrosis occurs more frequently in children than in adults, and it comprises a larger percentage of the nephritides in the former than in the latter. Clausen, 1925, observed 125 cases of nephritis in children, of which 102 were classed as hemorrhagic (glomerular) and 23 as parenchymatous (lipoid nephrosis). In general, the age distribution corresponds to that of glomerulonephritis.

Onset. The symptom that brings the patient to the physician is usually edema, but there is often a prodromal period of weakness, loss of appetite, and general malaise which precedes the onset of edema. Schwarz and Kohn, 1922, considered the absence of preceding infection an important feature of the disease. Blackfan, 1926, found an initial acute infection in only two of fourteen cases. He contrasts nephrosis with acute glomerulonephritis in this respect. Van Slyke, 1930, found

three out of nine cases in which infection seemed to play a rôle. However, other writers do not consider the absence of preceding infection a distinctive feature. Davison and Salinger, 1927, stated that the onset may be with or without a preceding infection. The initial infection is usually in the upper respiratory tract. Aldrich, 1926, found that three of seven cases of nephrosis were preceded by a cold and that colds often cause exacerbations. Lyttle and Rosenberg, 1929, found a history of infection in six out of eight patients. They consider persistent or recurrent infection the chief cause of chronicity. Apparently there is a history of preceding infection less frequently in nephrosis than in acute glomerulonephritis, but there is no sound reason for excluding a case from this group because it follows an acute infection.

Hematuria All investigators who regard nephrosis as distinct from glomerulonephritis are agreed that no case with hematuria should be classed as pure nephrosis, although the majority would accept in this group cases with a slight increase of erythrocytes in the urine. Obviously the presence of a few erythrocytes does not exclude nephrosis, since Addis has shown that the urine of normal individuals commonly contains a few red cells. In the mixed type an increase of erythrocytes or even a gross hematuria is occasionally seen, but not as frequently as in acute glomerulonephritis. These differences with respect to hematuria indicate that the glomerular lesion of nephrosis is somewhat different from that of glomerulonephritis.

Albuminuria Severe albuminuria is

an essential feature of nephrosis. During the active periods of the disease large quantities of protein are excreted daily in the urine, but during remissions the amount becomes much less, and the urine may even become normal. The urinary protein is about 85 to 90 per cent albumin and the rest chiefly globulin (Van Slyke, Geil). As the albuminuria continues, the plasma proteins decrease. Corresponding with the greater loss of albumin in the urine there is a much greater decrease of plasma albumin than of globulin. It is highly probable that this depletion of the blood proteins is the basic disturbance in nephrosis which gives rise to the distinctive clinical features that set it apart as a special type of nephritis.

There is no doubt that the urinary proteins are derived from the plasma proteins. This is indicated by the high proportion of albumin in the urine and the corresponding decrease of plasma albumin. The plasma proteins are excreted by the kidneys.

Does this excretion take place through the tubules or through the glomeruli? In instances of severe albuminuria microscopic sections of the kidneys show the capsular spaces distended with protein precipitated by the fixing reagent. This can hardly be interpreted as a reflux from the tubules since it is too widespread and uniform, and it is occasionally seen in the capsular space when there is none in the adjoining part of the tubule. Brier, 1931, has shown that bicloride injections cause albuminuria in glomerular fish, but not in those with glomerular kidneys. The evidence is incon-

vincing that protein is excreted through the glomerular capillaries

Is the excretion due to injury of the glomerular capillaries, or to alterations in the plasma proteins themselves? Since normal kidneys excrete foreign protein readily, it is conceivable that the plasma proteins may be so altered by toxic substances that they are treated by the kidney as foreign protein. This seems to be what Epstein had in mind when he called nephrosis "albuminuric diabetes." This theory is supported by Andrews, Thomas and Welker, 1929, who consider albuminuria "a detoxicating mechanism for eliminating poisonous products of protein metabolism" and not primarily due to disease of the kidneys. They believe that the normal plasma proteins are so altered by combination with toxic substances that they behave as foreign proteins. According to this view it is not necessary to assume an injury of the glomerular capillaries.

But this theory is highly improbable. There are many forms of albuminuria which must be ascribed entirely to capillary injury. Simple passive congestion of one kidney causes albuminuria of the affected organ only. When the renal artery is clamped for from 30 to 60 minutes and then released a severe albuminuria results from the temporary ischemia. The urine from the other kidney is normal. Orthostatic and bedotic albuminuria depend upon circulatory disturbances in the kidney. In glomerulonephritis and the mixed type of lipoid nephrosis there is considerable evidence of capillary injury. In the light of all this it is not necessary to im-

buminuria of pure lipoid nephrosis. Furthermore, Hewitt, 1929, has shown that purified plasma and urine albumin in nephrosis and nephritis exhibit a corresponding rotatory power indicating that they are identical. The evidence is fairly convincing that the albuminuria of both types of lipoid nephrosis is due to injury of the glomerular capillaries, even though one may be unwilling to accept the anatomical evidences of such injury.

The albuminuria of nephrosis is not different from that of glomerulonephritis except that it is often more severe and more frequently cyclic in character. Severe albuminuria is frequently seen in acute glomerulonephritis and in active chronic glomerulonephritis. The amount of albumin in the urine tends to decrease as the kidneys become contracted, probably because the capillary surface available for filtration decreases. The protein is decreased by the same factors that reduce the crystalloids.

Edema. Marked edema is an essential feature of nephrosis. It is a prominent initial symptom and often the most important cause of the patient's discomfort. Like albuminuria, it is intense in the active stages and slight or absent in the remissions. Edema is by no means peculiar to nephrosis. It occurs in glomerulonephritis, eclampsia, and amyloid disease of the kidneys. It is sometimes severe in acute and subacute glomerulonephritis, but is usually not prominent in the chronic stage. It tends to decrease as renal insufficiency develops, but some edema is usually present at times in the late stages. Renal disease with severe edema may be lipoid nephrosis,

acute or subacute glomerulonephritis, or amyloid disease of the kidneys. When severe renal edema is present, one may safely conclude that the kidneys are not contracted, but the exact structural changes cannot be inferred with certainty.

Epstein has shown that one of the most important causes of renal edema is the decrease of the plasma proteins, which lowers the osmotic pressure of the blood and causes an increased flow of fluid from the blood into the tissues. Edema usually occurs when the total protein falls below five per cent, or the albumin below two per cent, and it is nearly always present when the albumin falls below one per cent. The loss of plasma albumin lowers the osmotic pressure much more than the loss of a corresponding percentage of globulin, since the molecules of the former are much smaller. Edema may be produced experimentally by repeated bleeding of an animal until the plasma protein falls to a low level (Leiter, Barker and Kirk, Kumpf). There is no loss of albumin in the urine in this experiment. The kidneys remain normal.

The decrease of plasma protein is, however, not the only factor in renal edema. In acute glomerulonephritis edema develops before the plasma proteins have decreased. Also in lipoid nephrosis edema may develop or disappear while the plasma protein level remains unchanged. It is influenced by the fluid and salt intake and by intercurrent infections.

It is widely believed that renal edema is due to disease of the tubules. This is evidently the opinion of those who speak of "tubular nephritis" and

"nephritis with a nephrotic tendency." It is supposed that a nephrotic element (tubular injury) is superimposed on an inflammatory glomerular lesion. But there is no evidence to support this theory. The renal disease in which tubular injury is most severe, viz., bichloride of mercury nephrosis, shows no edema at all or only a trace. In chronic glomerulonephritis, in which edema is usually not conspicuous, the tubular injury is much more extensive than it is in lipoid nephrosis. A majority of the tubules are in various stages of atrophy, and the persistent ones show the same accumulations of lipoid and hyaline granules as are seen in lipoid nephrosis. Fahr states that the tubular injury in nephrosis may proceed to necrosis of the tubule and subsequent atrophy of its glomerulus. In the preparations which I have studied, however, the only lesion which leads to destruction of a tubule is closure of the capillaries of its associated glomerulus. The functional disturbances in "tubular nephritis" are due to escape of plasma proteins through the glomeruli.

Decrease of Plasma Proteins. The loss of protein in the urine (albuminuria) soon leads to depletion of the plasma proteins. Albumin is decreased more than globulin since it is excreted in much greater quantity. Possibly the smaller albumin molecules escape through the glomerular capillaries more readily than the larger globulin molecules. When the total plasma protein is low the globulin exceeds the albumin because less globulin is excreted and because globulin is more rapidly regenerated than albumin. The retention of protein decreases to a limited

been discussed above. It is possible that depletion of the plasma proteins is also responsible for lipemia and other systemic disturbances in lipoid nephrosis. Decrease of plasma proteins is not peculiar to pure lipoid nephrosis. It occurs also in the nephrotic type of glomerulonephritis (Fahr and Swanson, 1926, and Linder, Lundsgaard and Van Slyke, 1924) and in amyloid renal disease. The occurrence of this phenomenon in lobar pneumonia is not understood.

Lipemia. An increase of fats in the blood is usually found in lipoid nephrosis. The degree of lipemia is very variable but corresponds in a general way with the intensity of edema and albuminuria. Kumpf, 1931, produced lipemia as well as edema in rabbits by repeated bleedings—a result which suggests that depletion of the plasma proteins is a causal factor in lipemia. The greater part of the fat in the blood is neutral fat. Lipemia occurs also in glomerulonephritis when albuminuria and edema are conspicuous, but it disappears as the disease progresses toward uremia.

Hypertension. Hypertension is considered peculiar to nephritis and incompatible with pure nephrosis. When it is associated with a clinical picture otherwise typical of lipoid nephrosis, the disease is considered a mixed type or lipoid nephrosis. It is supposed that nephrosis has been superimposed on nephritis, or vice versa. Difficulties arise in the diagnosis of cases with moderate or slight elevations of blood pressure. The blood pressure may be normal on admission and rise later, or it may first become elevated and then fall for a few days.

of life. Occasionally the blood pressure remains at normal levels for several months, and then gradually becomes definitely high. Are cases of this type pure nephrosis or the mixed form? There are many borderline cases in which the distinction between pure and mixed lipoid nephrosis on the basis of blood pressure becomes somewhat arbitrary.

The elevation of blood pressure in nephritis is probably due to increased resistance to the flow of blood through the kidneys. Increased resistance may be caused by spastic or organic narrowing of the arterioles, or by obstruction of the glomerular circulation. In lipoid nephrosis with hypertension there is seldom any disease of the arterioles, but the glomerular capillaries are definitely narrowed by thickening of the basement membrane, and by endothelial increase. In a previous publication, 1929, I have described and illustrated this lesion.

Renal Insufficiency. The absence of evidence of renal insufficiency is an essential part of the concept of pure nephrosis. Even a slight nitrogen retention in the terminal stages is sufficient to exclude the case from the group of pure nephroses, according to the views of many writers. But some impairment of renal function is often demonstrable in nephrosis without hypertension if the function is studied thoroughly in the terminal stages. Van Slyke found a definite decrease of function, as measured by the urea clearance test, in eight of ten cases of "degenerative renal disease." Most of these were instances of lipoid nephrosis without hypertension. Three of his patients died typical uremic

deaths Schreyogg, 1931, includes as "genuine nephrosis" three patients in whom the non-protein nitrogen was at times 70 to 75 mgm per 100 cc of blood. If one excludes from pure nephrosis all cases with any impairment of renal function, one is more apt to exclude a case that has been studied thoroughly than one with incomplete data. A single determination of blood urea nitrogen does not establish the status of renal function.

A number of investigators report instances of typical pure nephrosis which later develop the features of glomerulonephritis, viz., nitrogen retention, uremia, hypertension. Shapiro, 1930, reported a pure nephrosis that later developed pool concentration (1007 to 1010), low phenolsulphonphthalein excretion (two per cent), and slight nitrogen retention. The blood pressure was never elevated. Contracted kidneys were found post-mortem. Lyttle and Rosenberg, 1929, cite a pure nephrosis in a boy eleven years old, which within two months became typical acute glomerulonephritis with hypertension and nitrogen retention. Other instances in which the clinical picture shifted from nephrosis to nephritis are reported by Mason, 1926, and Christian, 1929. It is, therefore, well established that the clinical picture of pure lipoid nephrosis may pass over into that of typical glomerulonephritis.

Contracted Kidneys from Nephrosis
Fahr believes that nephrosis may progress into a contracted kidney. Mackay and Johnston, 1930, and Ehrlich, 1930, describe a case of nephrosis of 17 years duration. There was no nitrogen retention and no hypertension but a

definite impairment of renal function was indicated by the low phenolsulphonphthalein output. Death was due to peritonitis. The kidneys were greatly enlarged (300 gm each) and fatty, and about half of the glomeruli showed various stages of hyaline degeneration. Ehrlich considers tubular degeneration the primary lesion.

Clinical Course Nephrosis with definite hypertension or renal insufficiency, i.e., the mixed type, may progress to uremia, but death usually results from infection or some other cause before the blood metabolites have reached the uremic level. Nephrosis of pure type, or with only minor deviations from this clinical picture, rarely ends in uremia. Some cases recover after a duration of months or years. The disease is cyclic in character, periods of albuminuria and edema alternating with remissions during which the patient is greatly improved. The mortality is higher than in acute glomerulonephritis, and death is usually due to infections, the most frequent of which is pneumococcic or streptococcic peritonitis. Erysipelas is next in frequency.

The Role of Infection It was stated above that many authors are unwilling to admit that pure lipoid nephrosis may have its onset following an infection, their objections being based in part at least upon the theory that the disease is not of infectious origin. The onset following an infectious process is admittedly infrequent, but it can hardly be doubted that it occurs occasionally. All writers are in agreement that low resistance to infection is characteristic of the disease. Cerebral sore throat often causes the "pre-

ance of edema and albuminuria in a patient temporarily free from these symptoms. Peritonitis is a frequent complication not only as a terminal infection but at any time during the course of the disease (Schwarz and Kohn, 1926, Eckstein, 1926). It may persist for a long time, and the patient may survive one or more attacks. The organisms found in the ascitic fluid are usually pneumococci, but often streptococci.

Of great interest are the remarkable observations of Schwarz and Kohn, 1926, that a bacteriemia is present from time to time in nephrosis. They observed this in six out of nine patients studied. Such persistent infections as these authors describe suggest that infection may play a primary rôle in lipoid nephrosis. Since infection frequently causes a recurrence of the disease, why may it not be responsible for the first attack?

PATHOLOGICAL ANATOMY

In both types of lipoid nephrosis the kidneys are large and yellowish, and their external surfaces are smooth. The tubules are filled with lipoid droplets. There are no essential differences in the tubular lesions in the two forms of nephrosis. In nephrosis of mixed type the glomerular lesions are convincing and easily recognized. (Figures 1, 2, 3). In sections stained with hematoxylin and eosin it is seen that the capillary walls are thick and somewhat hyaline in appearance but the increase in endothelial nuclei is not impressive. With the iron-haematein stain it is seen that the capillary walls are thickened and that there is an increase in the width of the basement membrane.

In some instances there are a great many endothelial nuclei, but usually the increase is not prominent. When death occurs, as it usually does, before the disease has progressed to definite renal insufficiency, this is the usual microscopic picture. It differs from typical chronic glomerulonephritis in that there is little or no tubular atrophy and that the glomerular lesion is chiefly a thickening of the capillary basement membrane. However, when the disease has progressed to uremia, a great many hyaline glomeruli with atrophic tubules are seen. A study of the different stages in the formation of a hyaline glomerulus shows convincingly that the hyaline condition is brought about by a progressive thickening of the capillary basement membrane. The lesion is clearly primary in the glomerulus since it is prominent there before the tubule begins to undergo atrophy. A moderately contracted kidney may develop from the mixed type of lipoid nephrosis. It differs from the contracted kidney of typical glomerulonephritis in that the hyaline glomeruli arise chiefly from thickening of the capillary basement membrane and not from endothelial proliferation as in the latter. However, in typical glomerulonephritis some of the glomeruli are obliterated in the same way as in nephrosis.

In pure lipoid nephrosis, as well as in instances with only minor deviations from this picture, most authors describe the glomeruli as normal. This observation has been made so frequently that normal glomeruli are now generally considered as an essential feature of lipoid nephrosis, and there is a tendency on the part of some au-

thors to exclude instances with abnormal glomeruli from this group Wohlbach and Blackfan, 1929, found slight glomerular lesions in their cases but attributed them to the associated peritonitis

The idea that the glomeruli are entirely normal in pure nephrosis began with Fahr, 1914. However, Fahr later modified his view somewhat. In his article in the Henke-Lubarsch Handbuch, 1925, he describes and illustrates very striking glomerular lesions in a case which shows nothing inconsistent clinically with pure nephrosis. His

illustrations are made from sections stained with hematoxylin and eosin but they evidently represent hyaline thickenings of the basement membrane such as I have described, 1929. Fahr at first attributed the glomerular lesions to tubular disease, but later he stated that the glomerular lesion is primary. He insists, however, that the glomerular lesion is degenerative (glomerulonephrosis) and distinct from glomerulonephritis, and he believes that glomerulonephrosis may lead to tubular atrophy and a contracted kidney. Evidently Fahr still believes that nephrosis



FIG. 1 Hydropic or nephrotic type of chronic glomerulonephritis. The tubules are large and pale and the external surfaces are smooth. Note that the tubules are intact and somewhat atrophic. The glomeruli are not enlarged and there is no increase in size of them. The glomerular capillaries are very small in some lobules and somewhat enlarged in others. There are no hyaline glomeruli. Hematoxylin and eosin.

is a degenerative disease, but he apparently no longer maintains that the nephrotic contracted kidney results from tubular degeneration.

Aschoff, 1927, stated that there are glomerular as well as tubular lesions in lipid nephrosis, but gives no detailed observations

In 1929, I made a detailed histological study of the glomeruli of four cases of nephrosis which showed only minor variations from the clinical picture of pure lipid nephrosis. These showed increase of endothelial cells or irregular thickenings of the basement membrane. It has been objected, how-

ever, that my cases were not examples of pure nephrosis. Since that time I have had the opportunity of studying three cases of nephrosis which fulfill the most rigid requirements of the pure type. Two of these cases were kindly furnished me by Dr Klemperer of New York City. In one of these the glomeruli showed a marked irregular thickening of the basement membrane and a definite increase in the size of the endothelial cells. The lesion is more pronounced than in the four cases published by me in 1929. In Dr Klemperer's second case there is no definite increase of endothelial cells,



FIG. 2. A glomerulus from the preceding case. Azocarmine stain. Note the irregular thickening of the capillary basement membrane. The glomerular epithelium is normal. There is no increase of endothelial nuclei. The narrowing and irregularity of the capillary lumen is due to thickening of the capillary basement membrane.

and the changes in the basement membrane are only slight. The third case, furnished me through the courtesy of Dr. Amberg of the Mayo Clinic, shows patchy thickenings of the capillary basement but no increase of endothelial cells.

It must be admitted, therefore, that there are instances of lipoid nephrosis in which the anatomical evidence of injury to the glomerular capillaries is only slight and perhaps not convincing. It is highly probable, however, that if the various investigators would use a stain that demonstrates the capillary

basement membrane the reports of normal glomeruli would be much fewer.

Wolbach and Blackfan observed slight inflammatory changes in the glomeruli in nephrosis, but attributed them to the associated peritonitis. This interpretation cannot be disproved, yet there is evidence of disturbed glomerular function before the development of peritonitis. Also, the glomerulitis that one occasionally finds with peritonitis usually shows many polymorphonuclear and mononuclear leucocytes.



FIG. 3. Hydropic or nephrotic type of chronic glomerulonephritis. Derived from a case of chronic glomerulonephritis. There are many hyaline glomeruli with atrophic tubules. High magnification of a glomerulus. Azocarmine stain. Note the extreme thickening of the capillary basement membrane with narrowing and occlusion of the capillary lumen. The thickened basement membrane shows numerous fenestrations.

ETIOLOGY AND PATHOGENESIS OF NEPHROSIS

(a) *Extra-renal Origin* At the present time a majority of authors subscribe to the view that the primary cause of nephrosis is some metabolic disorder. Because of the lipemia and the fatty infiltration of the renal tubules some believe that the primary disturbance is in fat metabolism. Others, impressed by the great loss of plasma protein, believe that the basic trouble is in protein metabolism, or that it is due to toxic alterations of the plasma proteins which lead to their excretion by the kidney. The changes in the kidneys are considered secondary to the metabolic disorder; and it is contended that the renal lesion is not severe enough to produce such widespread disturbances. It is also maintained that patients with nephrosis have a very low resistance to infection and readily develop nephritis as a secondary complication.

In preceding paragraphs strong evidence has been cited, indicating that the plasma proteins are identical with the urine proteins and that they are not altered in any way. We can explain the excretion of protein only on the assumption of injury of the glomerular capillaries, even in instances where there are no histologic evidences of injury. The excessive loss of plasma protein may well be responsible for the various manifestations of lipoid nephrosis. It is, no doubt, largely responsible for edema, and Kumpf, 1931, has shown that repeated bleeding of the glomerular capillaries leads to a lipoid nephrosis.

The interpretation of the primary cause of nephrosis is based upon

anatomical evidence. No other organ shows alterations of structure or function consistently. The tubules are filled with lipid droplets, and plasma proteins escape through the glomerular capillaries. But there are two theories as to the nature of the renal lesion.

One group of authors maintains that it is a degenerative lesion affecting only the tubules. Others admit that the glomeruli may be involved, but consider the glomerular lesion degenerative in character and distinct from glomerulonephritis (Fahr). A few consider it a form of glomerulonephritis.

The theory that the disease is limited to the tubules has very little in its favor. The protein escapes from the glomeruli. The tubules are filled with lipid droplets but they are less involved than in glomerulonephritis. When the tubules undergo atrophy it is a result of obstruction of their associated glomeruli. They do not become necrotic. It is difficult to believe that so mild a tubular injury could produce the clinical phenomena of nephrosis.

The theory that the glomerular injury is degenerative and not inflammatory in nature cannot be dismissed lightly. The chief structural change is thickening of the capillary basement membrane—a lesion that is also found in eclampsia (Bell, 1931) and in primary hypertension (McGregor, 1930). Whether this is interpreted as inflammatory or degenerative depends upon how inflammation is defined. An increase of endothelial nuclei is often found in both types of lipoid nephrosis. It is much less marked than the endothelial proliferation of typical

glomerulonephritis, but it is presumably an inflammatory reaction in both instances

The theory that lipoid nephrosis is a distinct entity meets with great difficulties in explaining the nature of the mixed type which is generally admitted to be a form of glomerulonephritis. The advocates of this theory have no difficulty in superimposing nephrosis on nephritis, or nephritis on nephrosis. They are not in agreement as to whether nephrosis is the main disease or the appendix, although the basic conception is radically different. Volhard and Fahr considered nephritis the main disease and nephrosis the appendix, but most of their followers have reversed the sequence apparently without realizing the radical departure from Volhard and Fahr's conception.

Edema is a general feature of nephritis. There is no logical basis for the assumption that every nephritis with edema has a nephrotic component. On the other hand, it is equally difficult to believe that almost all cases of nephrosis have a nephritic component. The nephritic appendix may be a slight hematuria, a temporary hypertension, or a moderate functional impairment, or one or more of these symptoms may be pronounced. The nephrotic syndrome is too closely connected with nephritis to be an independent entity.

The theory that lipoid nephrosis is a form of glomerulonephritis is based upon both clinical and anatomical evidence. Clinically there is the gradual blending of pure nephrosis with nephrotic glomerulonephritis. If one uses delicate functional tests it is difficult to find a case without some impairment of renal function (Van Slyke). An initial clinical picture of nephrosis

may pass over into that of nephritis. One is rarely certain of the diagnosis of pure nephrosis during the life of the patient. On the anatomical side, there is evidence of alterations of the walls of the glomerular capillaries in some instances of pure nephrosis and in all well-defined examples of the mixed type. The glomerular lesions are of the same type in both forms of nephrosis, but are much less pronounced in those that correspond to or approach the pure type. The lesions in the glomeruli are not identical with those of typical glomerulonephritis, since in nephrosis thickening of the basement membrane is usually more conspicuous than endothelial proliferation, but one often finds glomeruli with thick basement membranes in typical glomerulonephritis.

It is reasonable to suppose that the glomerular capillaries are first injured by some toxic substance of bacterial origin. When no reaction occurs in the capillaries, the phenomena of nephrosis develop, but when a reaction occurs (thickening of the basement membrane, endothelial proliferation) the symptoms considered characteristic of nephritis develop. When only a little reaction occurs, the patient presents slight variations from the picture of pure nephrosis. When the lesion progresses to the point of complete obstruction of the capillaries the glomerulus becomes hyaline, its tubule undergoes atrophy, and a form of contracted kidney develops.

It is possible that the toxic substance responsible for the capillary injury is somewhat different in nephrosis and nephritis. Pneumococcus seems to play a more important role in nephrosis.

It is widely believed that infection is not the primary cause of nephrosis since the onset is usually not preceded by an infectious process, yet there is abundant evidence that relapses are caused by infection. Randerath reported two cases in which severe infection preceded the renal symptoms, and Schwarz and Kohn have shown that bacteriemia occurs from time to time during the course of the disease. It has been shown that peritonitis may last for several months, causing a persistence of symptoms. In certain instances, at least, latent infection appears to be a primary cause of the renal symptoms and not merely a secondary factor.

SUMMARY

Two forms of chronic glomerulonephritis are recognized: an azotemic type characterized by nitrogen retention, and an hydropic or nephrotic type characterized by marked edema and albuminuria. There are numerous transitions between these groups clinically. In the nephrotic type the kidneys are usually large and fatty, while in the azotemic type they are commonly contracted.

The hydropic type, now called lipoid nephrosis, is often subdivided into pure lipoid nephrosis and a mixed type (nephritis with a nephrotic component). The pure differs from the mixed type in the absence of hematuria, hypertension, and impaired kidney function.

When the rough and repeated studies of the case have rarely seen a case that corresponds to the rigid definition of pure lipoid nephrosis, it is probable that the pure type is a distinct entity.

Edema is a general feature of nephritis. There is no basis for the belief that every nephritis with edema has a nephrotic component.

If nephrosis be a distinct entity, nearly all cases of nephrosis have a nephritic component.

In well-defined instances of the mixed type of lipoid nephrosis there is a marked thickening of the capillary basement membrane in the glomeruli and a variable amount of endothelial proliferation. Lesions of this type, but much less pronounced, are found in some instances of pure nephrosis as well as in nephrosis with slight variations from the pure type.

The theory is proposed that the primary disturbance in both nephrosis and nephritis is an injury of the glomerular capillaries by some toxic substance. If little or no reaction occurs in the capillaries the clinical picture of pure nephrosis develops; a moderate reaction produces some of the symptoms assigned to nephritis, viz., hematuria, hypertension, impaired kidney function, a marked reaction gives the clinical picture of nephritis.

The clinical picture depends in large measure on the character of the injury in the glomerular capillaries. When they are open and allow albumin to escape in large quantities, nephrosis develops. When they are narrowed or occluded, there is not much loss of albumin but hypertension and nitrogenous waste.

Lipoid nephrosis is not a distinct entity but a form of glomerulonephritis.

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BIBLIOGRAPHY

- ADDIS, T The number of formed elements in the urinary sediment of normal individuals, *Jr Clin Invest*, 1926, **11**, 409-415
- ALDRICH, C A The treatment of nephrosis, *Am Jr Dis Child*, 1926, **xxxii**, 163-182
- AMBERG, S Nephrosis in childhood, *Jr Am Med Assoc*, 1931, **xcvii**, 1048-1052
- ANDREWS, E, THOMAS, WM A, and WELKER, W F Albuminuria in the mechanism of detoxification, *Arch Int Med*, 1929, **xliii**, 139-143
- ASCHOFF, L Disorders of the kidneys with symptoms of Bright's disease, *Guy's Hosp Rep*, 1927, **lxxvii**, 314-324
- BARKER, M H, and KIRK, E J Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, *Arch Int Med*, 1930, **xlv**, 319-346
- BELL, E T Lipoid nephrosis, *Am Jr Path*, 1929, **v**, 587-622
- BELL, E T Renal lesions in the toxemias of pregnancy, *Am Jr Path*, 1932, **viii**, 1-42
- BIETER, R N Albuminuria in glomerular and aglomerular fish, *Jr Pharm and Exper Therap*, 1931, **xliii**, 407-412
- BLACKFAN, K D Acute nephritis in children, with special reference to the treatment of uremia, *Johns Hopkins Hosp Bull*, 1926, **xxvix**, 69-90
- CHRISTIAN, H A Nephrosis A critique, *Tr Assoc Am Physicians*, 1929, **xliv**, 68-76
- CLAUSEN, S W Parenchymatous nephritis *Am Jr Dis Child*, 1925, **xxix**, 581-586
- DAVISON, W C, and SALINGER, R Tubular nephritis (nephrosis) in childhood and its relationship to other forms of nephritis, *Johns Hopkins Hosp Bull*, 1927, **xl**, 329-353
- EHRLICH, W Lipoid nephrosis of unusual duration, pathologic-anatomic report, *Arch Int Med*, 1930, **xlv**, 749-759
- EPSTEIN, A A Clinical types of chronic parenchymatous nephritis—their treatment and results, *Med Clin N Am*, 1920, **iv**, 145
- EPSTEIN, A A A contribution to the study of the chemistry of blood serum, *Jr Exper Med*, 1912, **xvi**, 719-731
- EPSTEIN, A A Further observations on the nature and treatment of chronic nephrosis, *Am Jr Med Sci*, 1922, **clviii**, 167-186
- EPSTEIN, A A Concerning the causation of edema in chronic parenchymatous nephritis, methods for its alleviation, *Am Jr Med Sci*, 1917, **cliv**, 638-647
- FAHR, G, and SWANSON, W W The quantities of serum albumin, globulin, and fibrinogen in the blood plasma in acute and chronic nephropathies, *Arch Int Med*, 1926, **xxxviii**, 510-526
- FAHR, T Handbuch der speziellen pathologischen Anatomie und Histologie, 1925, F Henke und O Lubarsch, **vi**, Teil 1, 222-236
- GEILL, T Klinische Untersuchungen über Albumin und Globulin im Blut und im Harn bei Nierenkranken, *Ztschr f klin Med*, 1929, **cx**, 334-381
- HEWITT, L F Urine proteins in nephrosis, pregnancy and myelomatosis, *Lancet*, 1929, **i**, 66-68
- KANTROWITZ, A R, and KLIMPFER, P Über Lipoidnephrose, *Virchows Arch f path Anat*, 1931, **cclxxx**, 554-564
- KUMPF, A E Experimental edema and lipemia produced by repeated bleeding *Arch Path*, 1932, **viii**, 415-432
- LEITER, L Nephrosis, *Med*, 1931, **x**, 135-242
- LEITER, L Experimental edema, *Proc Soc Exper Biol and Med*, 1928, **xxvi**, 173-175
- LEITER, L Experimental edema—further observations on the plasma proteins and blood cholesterol *Proc Soc Exper Biol and Med*, 1930, **xxviii**, 1092-1095
- LINDER, G C, LUNDSCHAFF, C, VAN SLAKE, D D, and STALLMAN, L Changes in volume of plasma and absolute amount of plasma proteins in nephritis *Jr Exper Med*, 1924, **xxxix**, 921-929
- HILLER, A, LINDER, G C, VAN SLAKE, D D, and STALLMAN, L The metabolism in nephritis *Jr Exper Med*, 1924, **xxxix**, 931-955

- LITTLE, J D, and ROSENBERG, L The prognosis of acute nephritis in childhood, *Am Jr Dis Child*, 1929, xxxviii, 1052-1063
- MCGREGOR, L Histological changes in the renal glomerulus in essential (primary) hypertension, *Am Jr Path*, 1930, vi, 347-366
- MACKAY, E M, and JOHNSTON, C Lipoid nephrosis, *Arch Int Med*, 1930, xlv, 734-741
- MASON, E H The life history of a case of nephrosis, *Internat Clin*, 1926, i, 163-176
- RANDFRATH, E Die Pneumokokkeninfektionen im Kindersalter und ihre Bedeutung für die pathologische Anatomie der Nierenerkrankungen im Kindersalter, *Ztschr f Kinderh*, 1927, xliii, 687-716
- SCHREFFLOGG, G Verlauf und Prognose der "genuinen Nephrosen", *Deutsch Arch f klin Med*, 1931, clxx, 58-71
- SCHWARTZ, H, and KOHN, J L Studies of nephritis in children, *Am Jr Dis Child*, 1922, xxiv, 125-159
- SCHWARTZ, H and KOHN, J L Bacteriemia and skin manifestations in lipoid nephrosis, *Am Jr Dis Child*, 1929, xxxviii, 762-774
- SHAPIRO, P F Lipoid nephrosis, *Arch Int. Med*, 1930, xli, 137-160
- THOMAS, WM A, SCHLEGEL, K W, and ANDREWS, E Urinary proteins not originating in blood, *Arch Int Med*, 1928, xli, 445-448
- VAN SLYKE, D D, et al Observations on the courses of different types of Bright's disease, and on the resultant changes in renal anatomy, *Med*, 1930, ix, 257-386
- VOLHARD, F, and FAHR, T Die Brightsche Nierenkrankheit, *Klinik, Pathologie und Atlas*, 1914, J Springer, Berlin
- WOLBACH, B S, and BLACKFAN, K D. Clinical and pathological studies on tubular nephritis (nephrosis), *Tr Assoc Am Physicians*, 1929, xlv, 77-120

The Occurrence of Cystinuria in Healthy Young Men and Women*†

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CYSTINURIA has been considered a relatively rare error of metabolism. Since the report of the first cystine calculus of the urinary tract by Wollaston in 1810, the number of observed cases has been surprisingly small. Kretschmer,¹ in a review of the occurrence of cystine calculi written in 1916, was able to find reports of only 107 cases of cystine calculi in a period of more than a century since Wollaston's original observation. The present author has reviewed elsewhere² the literature since 1920 and has summarized 71 cases of cystinuria, although calculus formation had not been observed in all of these.

Cystinuria in the past has usually been diagnosed by microscopic examination of the urine, the presence of the typical hexagonal plates of cystine crystals in a urinary sediment can hardly escape detection particularly if these are present in considerable numbers. The diagnosis of cystinuria has usually been made in connection with the examination of urines of patients presenting symptoms of renal colic or calculi of the genito-urinary tract. Cystinuria uncomplicated by calculus formation has been detected almost en-

tirely by examinations of the urine of relatives of patients who have been compelled to seek surgical aid for the removal of calculi.

It seems probable that cystinuria uncomplicated by calculi may occur more frequently than is usually believed. Garrod³ states that Simon encountered one cystine sediment in 15,000 urines examined, and Primavera, one in 20,000. Sondern⁴ observed cystinuria in four urines of 35,000 specimens examined. It has been stated that only "2½ per cent of cystinurics develop stone, but the figure is probably high, on account of the large number of unrecognized cases of cystinuria."⁵ Since, as already stated, cystinuria has been diagnosed almost invariably in connection with the presence of calculi, the basis of such an estimate is not clear to the present author.

In view of the interest in the familial and genetic relationships of cystinuria and in view of the paucity of data concerning the frequency of cystinuria uncomplicated by calculus formation, it has seemed of value to report the results of a systematic clinical examination of more than 10,000 urines of young men and women, college students for the most part, for the presence of cystine. It is hoped that the

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present report, by demonstrating the feasibility of routine chemical examination of urine for cystine, may stimulate further work by others. Only when more data concerning the incidence and genetic relationships of cystinuria are available will a more perfect understanding of this anomaly, which presents so many surgical and medical problems, be made possible.

In recent years, two chemical tests for cystine which are simple and capable of clinical application have been suggested. The first and simpler of these is the cyanide-nitroprusside test, which has been used as a test for cystine for some years, but which does not appear to have been applied to the detection of cystine in urine extensively. This test depends upon the fact that cystine may be reduced to its sulfhydryl derivative, cysteine, by sodium cyanide and that cysteine, in the presence of sodium cyanide gives a brilliant magenta color with sodium nitroprusside. Brand⁶ has recently advocated the clinical use of this test in routine examination of urine, especially in cases of renal colic. We have carried out this test as follows: To 5 c.c. of urine, 2 c.c. of a 5 per cent sodium cyanide solution are added and the reaction is allowed to proceed for 10 minutes. A few drops (usually 5 drops delivered from a serological pipette of 1 or 2 c.c. capacity) of a 5 per cent solution of sodium nitroprusside are added and thorough mixing is secured. Both nitroprusside and sodium cyanide should be freshly prepared. Normal urines have a pale pink color, while cystinuric urines give a very faint pink color. The color is ob-

tained. Protein, if present in the urine, should be removed before testing, this can best be accomplished by heat coagulation and removal of the precipitate by filtration.

The color developed is similar to that obtained in the well known nitroprusside test for creatinine (Weyl) or acetone (Legal). However color production with these substances is obtained only in the presence of a stronger alkali, as sodium hydroxide. The cyanide-nitroprusside reaction is not specific for cystine or cysteine, but is given by any compound containing the sulfhydryl group ($-SH$) or by any compound which on reduction by cyanide is capable of yielding this sulfhydryl group.

A second *more specific* but less simply performed test is the naphthoquinonesulfonic acid test of Sullivan.⁷ We have carried out this test according to the directions of Sullivan. To 5 c.c. of urine, 2 c.c. of a *freshly prepared* 5 per cent aqueous solution of sodium cyanide are added; the solution is thoroughly mixed and the reduction is allowed to proceed for 10 minutes at room temperature ($20^{\circ}-25^{\circ}C$). One c.c. of a *freshly prepared* 0.5 per cent aqueous solution of 1,2-naphthoquinone-4-sodium sulfonate* is added, the contents of the tubes are carefully mixed, and immediately 5 c.c. of a 10 per cent solution of anhydrous sodium sulfite** in 0.5 N sodium hydroxide are added. The solutions are mixed and the reaction is allowed to proceed for 30 minutes at room

*This may be obtained from the Eastman Kodak Company, Rochester, New York.

**We have found Merck's C. P. (anhydrous) sodium sulfite satisfactory.

temperature After the addition of 1 c.c. of a 2 per cent solution of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_4$) in 0.5 N sodium hydroxide, a *pure red color* is obtained if cystine is present With other sulfur compounds and many other biologically important substances (amino acids, carbohydrates, acetone, etc.), a yellow color is obtained According to the extensive studies of Sullivan this reaction is more specific for cystine (or cysteine) than any of the other tests proposed

In our experience with parallel tests in which both of these reactions were carried out, a negative cyanide-nitroprusside reaction has never been observed in a urine with which the Sullivan reaction was positive Occasionally a weakly positive cyanide-nitroprusside reaction has been observed in a urine which showed a negative Sullivan test We would recommend therefore that the simpler cyanide-nitroprusside test be used in routine examinations of urine for the presence of cystine, but that all urines which show a positive reaction with this test should also be tested by the reaction of Sullivan A positive Sullivan test in the light of our present knowledge is definite evidence of the presence of cystine

Most of the samples of urine examined were obtained in connection with the medical examinations given to entering students at the University of Michigan in the fall of 1929, 1930 and 1931 We wish to express our appreciation of the cooperation of the members of the University Health Service, Dr. W. G. Forsythe and Dr. Margaret Bell, both at the time of the fall examinations and during later follow-up examinations Through the courtesy of Dr. Glenadine Snow and Professor Perry Brundage it was possible

to examine urines of about 1100 students at the Michigan State Normal College in the fall of 1930 and with the cooperation of Professor D. L. Randall we were able to examine 106 urines collected from male students at Albion College in the fall of 1929

The urines of a total of 10534 students have been examined (6253 men, 4281 women) We believe that the analysis of these data affords trustworthy information concerning the incidence of cystinuria in healthy individuals of the age group which includes the average student In almost every case in which positive tests for cystine were obtained, additional samples were examined at frequent intervals We have thus been able to study a considerable number of the group at intervals over a period of 30 months

The results may be summarized as follows In this series we have observed four individuals (three men and one woman) in whose urines cystine crystals have usually been present These urines presented the typical picture of cystinuria, have given strongly positive cyanide-nitroprusside and Sullivan tests, and, as shown later in the tables, the percentage of urinary organic sulfur was distinctly higher than normal, a characteristic of cystinuria In addition 14 individuals have been examined repeatedly in whose urines strongly positive tests by both cystine reactions were regularly obtained although cystine crystals have never been present in the urine* We consider this group as definitely cystinuric as the first and smaller group In none of these 18 individuals have we been

*In one individual (B. C. (T-1) c III, cystine was isolated from the urine.

able to obtain any history of the occurrence of calculi

The urines of a third group of 11 individuals have consistently shown weak tests for cystine by both the cyanide-nitroprusside and Sullivan reactions and in many of these urines the percentages of organic sulfur of the urine have been found to vary only slightly from the normal values. The urines of still a fourth group of 11 individuals have given occasional weakly positive color tests, particularly by the cyanide-nitroprusside reaction; but the sulfur distributions of these urines have been normal. There seems little doubt that cystinuria, in the sense of the excretion of abnormal amounts of the amino acid in the urine, may be of more common occurrence than is to be inferred from the reports of the finding of cystine calculi or cystine crystals in the urine.

In a further study of the first two groups, the distribution of urinary sul-

fur was determined in some instances. Under normal conditions, cystine arising from the catabolism of protein, either exogenous or endogenous, is oxidized almost completely and the sulfur present in the cystine molecule, oxidized to sulfuric acid, is excreted by the kidneys as sulfate sulfur. A small part of the total sulfur excreted in the urine is present as organic ("neutral") or unoxidized sulfur. There exists in normal urine a trace only of cystine. In the metabolic error, cystinuria, on the other hand, a very considerable part of the cystine formed in catabolism escapes oxidation and is excreted as such by the kidneys. Since the sulfur of the cystine molecule is in the unoxidized form (organic sulfur), a marked rise in the excretion of organic sulfur is observed as a characteristic of cystinuric urine.

In table I are presented studies of the distribution of the sulfur of normal urines for comparison. It will be ob-

TABLE I
PARTITION OF SULFUR IN NORMAL INDIVIDUALS

The results of analysis of all specimens not designated as 24 hour samples are calculated as grams per 100 cc of urine

NAME	PERIOD	TOTAL N	TOTAL S	TOTAL SULFATE S	ORGANIC S	
	HR.	GM.	GM.	GM.	GM.	Per cent of total S
C. A. A.	24*	12.13	0.758	0.688	0.070	9.2
J. A. S.	24	12.23	0.865	0.784	0.081	9.4
L. A. S.	24	8.24	0.677	0.605	0.072	10.6
C. M. V.	—	0.687	0.045	0.039	0.006	13.3
G. I. I.	24**	11.00	0.769	0.643	0.126	16.4
P. B.	—	—	0.104	0.088	0.016	15.3
A. V.	—	0.710	0.081	0.074	0.007	8.6
A. F.	—	1.76	0.135	0.116	0.020	14.7
A. C.	—	—	0.117	0.111	0.006	5.1
24 hr. samples		21.1	1.410	1.264	0.146	10.3
24 hr. samples		21.1	1.410	1.264	0.146	10.3

served that the organic sulfur comprises much less than 20 per cent of the total sulfur excreted, in most cases less than 15 per cent. In marked contrast to these values obtained for normal urines are the results of similar studies of individuals whose urine as indicated by positive Sullivan and cyanide-nitroprusside tests contained cystine (tables II and III). Values for organic sulfur as high as 40 per cent of the total sulfur excreted are commonly found and in a few individuals only does the percentage of organic sulfur fall below 20 per cent.

Particularly interesting are the results of the studies with S P presented in table II*. This subject was 17 years of age when first observed and

*In tables II and III, unless otherwise indicated, the quantitative estimations of cystine were made by the colorimetric method of Looney

has never failed to show marked cystinuria in about 25 examinations of the urine extending over a period of 18 months. Not only is the excretion of cystine very marked, but abundant cystine crystals have been present uniformly in the urine, particularly on standing. Figure 1 is a microphotograph of sediment from such a urine. This photograph was made from crystals obtained without centrifugation by means of a pipette from a urine about 30 minutes after the sample was voided. The sediment is shown to be almost pure cystine.

Despite this abundant excretion of cystine, no history of colic of the urinary tract or other indication of calculus formation has been obtained. The urine of an older brother of the patient has been examined for cystine with negative results. The analyses in the table include both 24 hour urines



FIG 1 Cystine crystals in the urine of subject S P

TABLE II
 THE PRESENTATION OF URINARY SULFUR IN ACUTE CYSTINURIA
 Subject, S. P., age 17 years

Date	Hours	Total N	Total S	Form S	Organic S	Cystine	Sediment
		Gm	Gm	Gm	Per Cent of Totals	Gm	
1-1-31	24	11.20	0.704	0.439	39.1	0.806 ¹ (0.143)	Many cystine crystals
1-1-31	24	13.00	0.786	0.527	33.0	0.856 (0.176)	Many cystine crystals
1-1-31	3	1.81	0.137	0.075	45.3	0.123 (0.005)	Occasional cystine crystal
1-2-31	3	1.77	0.126	0.066	47.6	0.136	No cystine crystals seen
1-1-31	24	12.60	0.774	0.481	37.9	0.920 (0.033)	Few cystine crystals
1-2-31	24	10.94	0.691	0.447	35.3	0.710 (0.214)	Many cystine crystals
1-2-31	24	12.67	0.862	0.527	38.8	—	Very few cystine crystals
1-2-31	3	—	0.066	0.033	50.0	—	Very few cystine crystals
1-11-32	3	1.62	0.120	0.062	48.3	0.156 ²	Occasional cystine crystals
1-20-32	8	3.46 ³	0.204	0.112	45.1	—	Occasional cystine crystals

¹Figures in parentheses indicate cystine present in sediment. This amount should be added to give the total daily cystine excretion.

²Urine of the three hour periods are morning urines, usually 8:45-11:45 A.M.

³Cystine determined by modified Okuda method.

⁴Night urine, 12:15-8:15 A.M.

and those excreted in shorter periods. The organic sulfur in urines collected over the shorter periods (three hours) appears to be higher than that of the 24 hour samples. This is undoubtedly due to the fact that much of the organic sulfur is not determined in the urines collected over the longer periods, since in these urines cystine, as shown in the tables, separates out and is not determined in the sulfur partition of the filtered urines.

Subject B C J (table III) is a boy of 11 years, who has uniformly shown large numbers of cystine crystals in the urine. An elder sister of this boy was operated upon for removal of cystine calculi and was definitely cystinuric.⁸ Repeated examinations of the urines of the father, mother, younger brother and four other sisters of the subject have failed to show cystinuria.

The urine of subject F P (table III) has always given strongly positive tests for cystine by both the Sullivan and cyanide-nitroprusside tests but in only one examination has the presence of cystine crystals in the urinary sediment been observed. This subject undoubtedly would not be recognized as a cystinuric on the basis of the usual examinations of the *urinary sediment*, but both *chemical tests* for cystine and the percentage of *urinary organic sulfur* indicate definitely a marked cystinuria. The case of H H (table III) is similar. In three examinations large numbers of cystine crystals were found in the urinary sediment, but the most recent examination of the urine failed to reveal cystine crystals. Despite this, the condition of cystinuria still persisted as is shown both by the intense Sullivan reaction given by the urine and by the high percentage of organic sul-

fur (44.1 per cent), a figure slightly higher than that previously observed in a study of this case.

The studies here reported serve to emphasize the fact that failure to detect cystine microscopically in the urinary sediment is not an adequate criterion of the absence of cystinuria. In clinical reports of cystinuria, the statement is frequently made that cystinuria is intermittent or that the cystinuria has ceased after operative removal of calculi. Reference is occasionally made to cystine calculi without cystinuria. These statements are based on the failure to detect cystine in the urine microscopically or on inadequate chemical tests for cystine. We have studied a case in which cystine calculi were removed at operation, but in which the presence of cystine crystals in the urinary sediment was detected microscopically in only one specimen of the urine.⁹ However, the urines at all times showed the presence of considerable amounts of cystine on *chemical examination*. Undoubtedly this case would have been cited in the past as an illustration of the cessation of cystinuria after operative removal of calculi.

Since chemical tests which are sufficiently simple to be adapted to clinical use, are now available for the detection of cystine, it is urged that each case of cystinuria and cystine calculus be studied carefully by the use of *chemical methods*. It is hoped that the data here presented may stimulate further study of this interesting but imperfectly understood error of metabolism. Only by carefully conducted study can we arrive at an adequate understanding of this disturbance of metabolism.

TABLE III
THE PARTITION OF URINARY SULFUR IN CYSTINURIA OF "HEALTHY" INDIVIDUALS

At the expiration of the 24 hour specimens of urine all results are expressed as grams per 100 cc of urine

Case	Date	Total N		Total S		Organic S		Cystine	Sullivan Test	Notes
		Gm	Gm	Gm	Gm	Per Cent of Total S	Gm			
P. P.	11-11-29	---	0.167	0.093	0.074	44.3	---	---	++++	Cystine isolated (Gaskell) Cystine crystals on a previous examination
H. H.	11-18-30	---	0.095	0.056	0.039	40.4	0.083	++++	++++	Cystine crystals abundant
H. H.	2-6-32	---	0.077	0.043	0.034	44.1	---	---	+++	No cystine crystals
P. C. I.	11-20-30	10.59*	0.613	0.425	0.188	30.7	0.605	++++	++++	Cystine crystals abundant Previous examination 56 mg cystine per 100 cc
H. C.	11-3-29	---	0.097	0.066	0.031	31.9	---	---	+++	Small amount of cystine isolated (Gaskell)
P. C.	11-18-30	---	0.057	0.044	0.013	22.8	---	---	+	
H. C.	1-8-31	0.85	0.047	0.033	0.014	29.9	---	---	+	

E. L. T	1-7-31	0.89	0.056	0.040	0.016	28.6	—	++	
E. L. T	1-10-31	12.19*	0.852	0.693	0.159	18.7	—	+	
I. L. T	1-17-31	1.30	0.094	0.072	0.022	23.4	—	+	
E. L. T	11-4-31	—	0.084	0.065	0.019	22.6	—	+++	
L. L. T	1-19-32	8.90*	0.624	0.454	0.170	27.2	—	++	
S. L.	12-1-30	—	0.029	0.016	0.013	44.8	—	+	4 previous examinations showed Sullivan test ++
D. W.	10-20-30	0.737	0.047	0.037	0.010	22.9	—	+	
D. W.	11-5-31	—	0.042	0.032	0.010	23.8	—	+	
M. S. D.	1-9-31	—	0.050	0.039	0.011	22.0	—	+	
C. B.	11-20-30	—	0.138	0.113	0.025	18.1	0.046	++	
H. P.	7-12-31	7.56*	0.518	0.425	0.093	18.0	0.103	++	Frequent previous examinations over 2 yr period Sullivan ++
I. C. W.	11-6-31	—	0.047	0.038	0.009	19.2	—	++	

*24 hour specimens of urine

We wish to express our appreciation of the cooperation of the staff of assistants who have assisted in the routine examinations of so many urines in a short period of time. In particular, credit is due to William T

Krebs, Robert W Virtue, Robert L Grant, and Svend Pedersen for their aid in the work. Grants from the Faculty Research Fund of the University of Michigan have made it possible to carry on this work.

REFERENCES

- ¹KRETSCHMER, H L Cystinuria and cystin stones With report of a new family of cystinurics Urol Cut Rev, 1916, xx, 1-10
- ²LEWIS, H B Cystinuria, a review of some recent investigations Yale J Biol Med, 1931-32, iv, 437-449
- ³GARROD, A E Inborn errors of metabolism London, 2nd Edition, 1923, 17 Oxford University Press
- ⁴SANDERN, E F Cystinuria Arch Diagn, 1911, iv, 267-269
- ⁵EDWARDS, H C Cystinuria with calculus formation Brit J Surg, 1924-25, xii, 345-350
- ⁶BRAND, E, HARRIS, M M, and BILLOON, S Cystinuria The excretion of a cystine complex which decomposes in the urine with the liberation of free cystine. J Biol Chem, 1930, lxxxvi, 315-331
- ⁷SULLIVAN, M X Studies on the biochemistry of sulphur II Further studies on the distinctive reaction for cysteine and cystine Pub Health Repts, 1929, xlv, 1421-1428
- ⁸KLOPFENSTEIN, A R, and LEWIS, H B Unpublished data.

Effects of the Administration of Glucose and Insulin on the Glycogen Content of Normal and Experimental Damaged Livers*†

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THE glycogen of the liver has a far reaching influence on the well-being of the body. Not only is the metabolism of carbohydrates, fats, and probably proteins disturbed when hepatic glycogen is drastically diminished, but the liver and the entire organism become more susceptible to toxic influences causing functional or organic damage. The glycogen content of the liver is reduced in diffuse injuries to this organ. This is true both of experimental animals after such procedures as administration of hepatic poisons or ligation of the common bile duct and of human beings suffering from diseases of the liver. A virtual disappearance of hepatic glycogen has been established in cases of acute yellow atrophy of the liver by Umber¹ and by Kimura.²

Evidence has accumulated to show that the amount of glycogen found in the liver at any given time represents the balance between continuous building up and release of this substance as glucose rather than the extent of its storage, analogous to that of fat. This

new conception is shifting the emphasis from a deficiency of glycogen to the underlying disturbance in carbohydrate metabolism of which glycogen, although representing only one link, is a very useful indicator. It is interesting that in experimental injury of the liver, simultaneously with the decrease in glycogen, there is an influx of fat with increased formation of intermediary substance, e.g., ketone bodies.³ Parallel with this goes a lowering of the blood sugar level and other disturbances of blood sugar regulation.⁴

From the point of view of clinical medicine it is important whether the faulty metabolism seen in diseases of the liver and expressed in a low hepatic glycogen can be favorably influenced by therapeutic measures. With this object oral and intravenous administration of glucose has been practiced for years, especially in cases of delayed chloroform poisoning and in acute yellow atrophy of the liver. Since the advent of insulin this hormone has been used in conjunction with glucose in many forms of hepatic disease.

Numerous reports of favorable curative or symptomatic results with the insulin-glucose therapy have emanated largely from German and French clinics regarding cases of acute yellow atrophy of the liver, especially

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jaundice, arsenical hepatitis, cirrhosis of the liver, lues of the liver, acute phosphorus poisoning, cholecystitis, and carcinoma of the liver⁵⁻¹⁴ As basis of this therapy the authors to whom reference has been made invariably mentioned an increase in the glycogen content of the liver after administration of insulin and glucose Since in the literature there are no data on the behavior of glycogen in damaged livers, this assumption rests on an analogy with certain observations on normal animals Only one medical writer, Ravdin,¹⁵ on theoretical grounds advises caution regarding the use of insulin in hepatic diseases

THE EFFECT OF GLUCOSE AND INSULIN ON THE GLYCOGEN OF THE NORMAL LIVER

It is a mooted question whether insulin favors the deposition of hepatic glycogen in the non-diabetic animal Depending on experimental conditions increase, no change, or decrease in the glycogen of the liver after insulin and glucose have been reported by different investigators the majority of whom performed no comparative experiments with glucose alone

Among the authors who report such control experiments Macleod¹⁶ found that the addition of insulin retarded the deposition of glycogen after glucose in starved animals with a low initial glycogen content of the liver In animals with an abundance of hepatic glycogen the insulin actually reduced the glycogen of the liver in spite of the addition of glucose Corn and Corn¹⁷ found no change in the glycogen content of the liver after insulin plus glucose in normal animals

From a complete balance sheet for ingested sugar they calculated that in the experiment without insulin three times as much of the given glucose was deposited in the form of glycogen as in the experiment with insulin.

Finally, Rubino, Varela and Collazo,¹⁸ who studied the hepatic glycogen in a series of rabbits over a period of twenty-four hours, found that after insulin and glucose there was a sharp rise in glycogen at the two-hour period followed by a rapid decline which ended in a level below that at the beginning of the experiment. On the other hand the animals which received only glucose exhibited an increased glycogen content of the liver throughout the twenty-four hours of observation

An explanation for such a decreased deposition of glycogen was offered by the Coris¹⁹ who found that under the influence of insulin more carbohydrate was oxidized leaving less to be deposited as glycogen When they increased the amount of glucose given to the insulinized animals to the point where their blood sugar was maintained on the same level as that of the animals which had received glucose alone, the same amount of glycogen was found in the livers in both groups According to this evidence the amount of glycogen deposited in livers of normal animals is a function of the height of the blood sugar.

In our experiments rabbits were given 0.5 units of insulin plus 2.5 gm of glucose per kgm of body weight and sacrificed three hours later for glycogen determinations* In normal animals there was an average increase of

*Laboratorial methods and protocols are given in the appendix, p. 4

hepatic glycogen from 5.8 per cent before to 8.5 per cent after the administration of insulin and glucose—a gain of 50 per cent

In order to test the effect of insulin and glucose on rabbits with a low glycogen content of the liver, comparable to that in animals with diffuse hepatic damage, they were starved for three days prior to the experiment. The hepatic glycogen, which was thus reduced to an average of 0.7 per cent, rose three hours after insulin and glucose to 2.3 per cent—an increase of 200 per cent

As a check on the preceding experiment the hepatic glycogen of a number of rabbits was reduced by administration of thyroxin. Each animal received subcutaneously over a period of five days a total dose of 7.7 mg. of this hormone per kgm. of body weight. These rabbits had an average of 0.65 per cent of glucose in the liver before, and 2.62 per cent after, receiving insulin and glucose—an addition of 300 per cent. A total of eighteen rabbits was used for these three experiments, the results of which are summarized in chart 1

From data of the quoted writers and the above figures, two conclusions are justified. (1) In normal animals insulin plus glucose decreases the glycogen content of the liver when this is high, effects at least a temporary moderate increase when the glycogen is neither high nor low, and stimulates a relatively large deposition when it is low. (2) Administration of glucose in equal amounts without insulin results in a greater increase of hepatic glycogen

THE EFFECT OF GLUCOSE AND INSULIN ON THE GLYCOGEN OF THE DAMAGED LIVER

In order to ascertain the action of insulin plus glucose on the experimentally injured liver, glycogen determinations were performed on four groups of rabbits. Animals in the first group received a single large dose of phosphorus, sufficient to cause death in about twenty-four hours. The experiments were carried out fourteen hours after the injection of the poison when the glycogen content of the liver was still relatively high. The average hepatic glycogen in this group was 4.7 per cent before and 1.66 per cent after the administration of insulin and glucose—a loss of 65 per cent

Rabbits in the second group were given daily small doses of phosphorus and the experiments were performed at a stage of poisoning when epinephrin ceased to produce a hyperglycemic blood sugar curve. This usually occurred after nine to twelve injections. The initial glycogen content of the liver in this group was quite low, averaging 1 per cent. Following insulin and glucose the hepatic glycogen was found to be further diminished to an average of 0.38 per cent—a reduction of 60 per cent. (Identical results were obtained in two rabbits with experimental cirrhosis of the liver due to manganese.)

In the third group the animals were given single large doses of chloroform to which about half of the animals succumbed during the first two days. The surviving rabbits were followed with the modified glucose tolerance test and the epinephrin test. The glycogen experiments were performed about ten

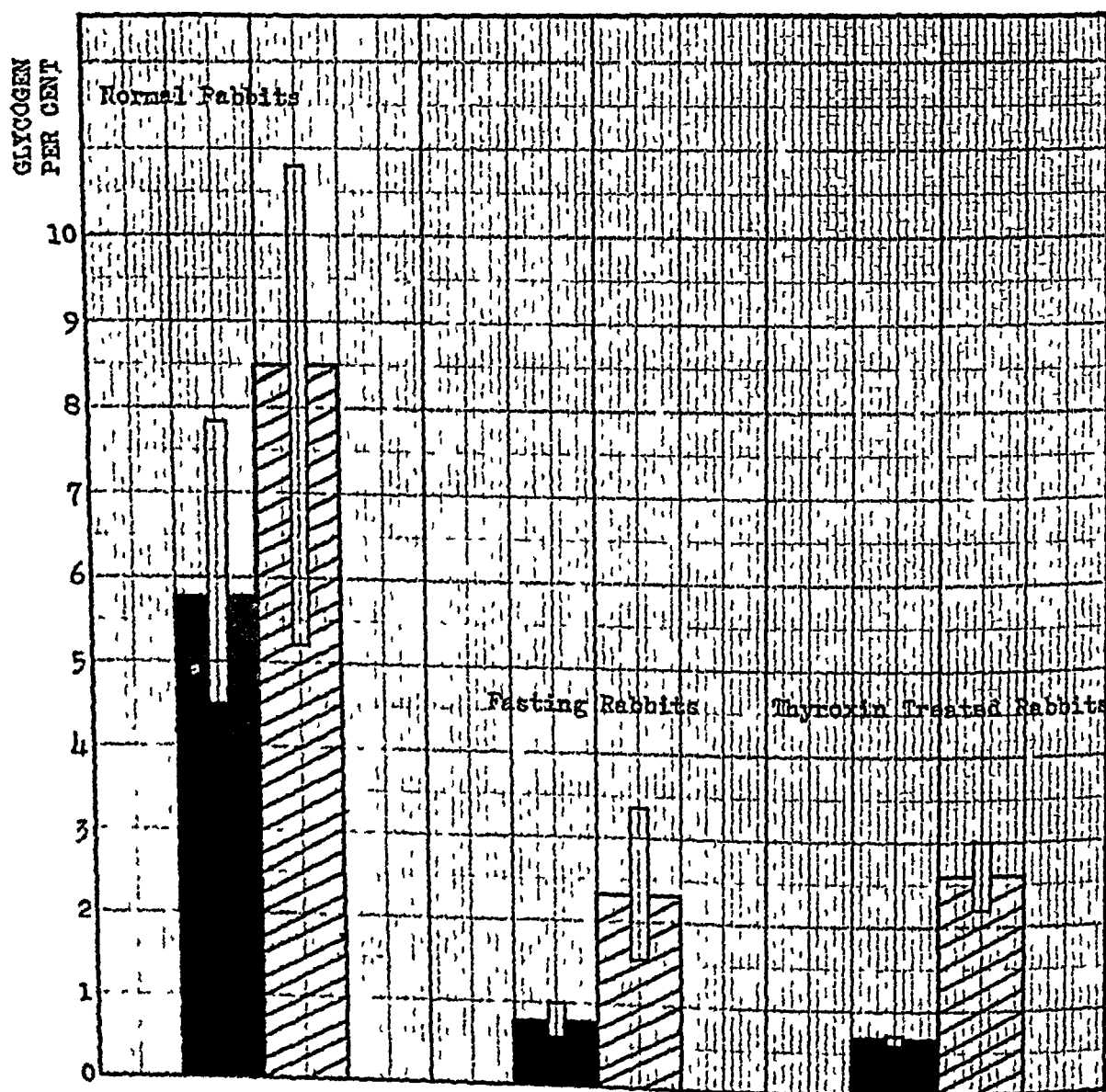


CHART 1. Glycogen content of the liver in normal, fasting, and thyroxin treated rabbits before (black columns), and after (cross-hatched columns), administration of insulin to a group of animals.

days following the poisoning after the hyperglycemic response to epinephrin had returned to normal and the glucose tolerance was normal or increased, probably due to active regeneration of the β cells. The glycogen in these animals was 23 per cent before, and increased to 45 per cent after and glucose tolerance was 14 per cent. The

results of these three experiments are shown in chart 2.

In a fourth group rabbits were given small daily doses of phosphorus, and glucose alone was administered on the tenth day. Unfortunately a severe winter had caused widespread coccidiosis among rabbits in California so that most animals obtainable had a few hepatic lesions due to this infection, which appreciably lowered their resistance to any affecting the liver and caused a greater variability of the

glycogen content Since this work will be repeated at a more favorable time it is sufficient to mention here that the average hepatic glycogen was twice as high in the rabbits which were sacrificed after having received glucose. Glycogen determinations were made in thirty-two rabbits belonging to these four groups

The reduction of hepatic glycogen after insulin and glucose in rabbits subjected to phosphorus poisoning is unlike the already mentioned lessened deposition of this substance in the Corris' normal animals. In their case the blood sugar of the insulinized animals was lower than that of the controls. In our case the blood sugar of the poisoned rabbits due to reduced sugar tolerance was higher than that of the normal controls. As shown in a previous paper⁴ the average blood sugar of

six rabbits computed from blood sugar curves over three hours after administration of insulin and glucose was 126 mg per cent before phosphorus injections were begun, and 140 mg per cent at the stage where glycogen determinations were made

Nor can the diminution in glycogen after insulin and glucose be explained on the bases of von Noorden and Isaac's theory of glycogen formation²⁰. According to this theory glycogenesis in the liver is dependent upon the existing supply of glycogen from which energy for the polymerization of glucose is derived through its transformation into lactic acid. In our experiments we see that a relatively high hepatic glycogen in acute phosphorus poisoning fails to prevent a decrease in glycogen. On the other hand a low glycogen content of the normal liver

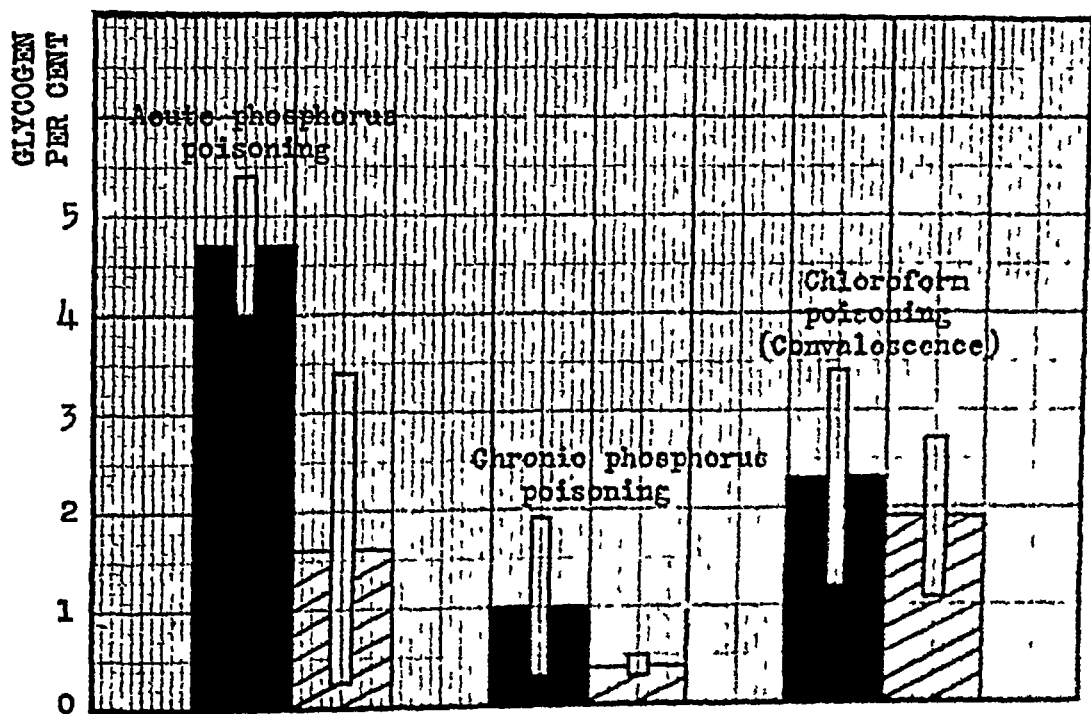


CHART 2 Glycogen content of the liver in rabbits poisoned with phosphorus, and chloroform before (black columns), and after (cross hatched columns), administration of insulin and glucose. The narrow, unshaded portion of each column represents the glycogen content in each group of animals

does not hinder accumulation of this substance as seen from the experiments with fasting and with thyroxin medication

The probable explanation of the decrease in glycogen of the damaged liver lies in the fact emphasized by Macleod²¹ that insulin in non-diabetic animals "distorts the whole of metabolism by overstimulating certain phases of it. The excess causes some parts of the metabolic machinery to go too quickly or too slowly for other parts upon which it has no influence. Such disorganization may lead to the accumulation of intermediary products of metabolism having a detrimental influence on the working of the machine as a whole." Such a disturbance of the metabolic equilibrium would be even more marked in animals with injury of the liver. In these animals the insufficiency of hepatic parenchyma is evidently such that they fail to compensate for greater glycogenolysis due to insulin by increased glycogenogenesis in spite of an excess of glucose in the blood.

That the liver under the conditions of our experiments still retains its power of glycogenogenesis is shown by the presence of some hepatic glycogen in every examined animal. To this can be added an increase in hepatic glycogen after administration of glucose which is to be seen in rabbits subjected to chronic phorus poisoning.

In rabbits recovering from chloroform poisoning the glycogen content of the liver is still low in spite of a normal blood glucose. Structural reorganization of the liver takes place to a certain extent, but the process is not complete. The glycogen content of the liver is still low in spite of a normal blood glucose.

crease in hepatic glycogen which, however, did not exceed the limits of experimental error, and therefore can be considered only as indicating that there was no rise in glycogen content. This, the last abnormality of carbohydrate metabolism to disappear during convalescence from chloroform poisoning, is explained by the work of Doljanski²² with cultures of hepatic tissue. This author showed that active proliferation of hepatic cells in vitro is antagonistic to glycogen accumulation, but that these cells could be made to fill with glycogen by artificially slowing their growth. The same is evidently true of a rapidly regenerating liver in vivo.

THE PLACE OF INSULIN IN THE THERAPY OF HEPATIC DISEASES

Having seen that insulin reduces the deposition of glycogen in the liver of normal animals and actually decreases the already small original amount of glycogen in the experimentally damaged liver in spite of administration of glucose, we are confronted with the question to what extent this knowledge can be applied to hepatic diseases in man. In answering this question two considerations are of importance. The first is the essentially uniform character of hepatic injury whether induced in experimental animals or spontaneously occurring in human beings. This conception, as discussed elsewhere,²³ is supported by microscopic evidence and by observations on the metabolic activity of the liver.

The second consideration is the similarity between the lesions of phorus and of delayed chloroform poisoning on one side, and subacute

yellow atrophy and catarrhal jaundice on the other. Incidentally it is in the last two diseases that the insulin-glucose therapy is being particularly advocated. For these reasons it is felt that the obtained data on the behavior of glycogen in experimentally injured livers have a bearing on diseases of the liver in man.

Let us turn now from the subject of hepatic glycogen to other evidence in favor of a beneficial action of insulin in diseases of the liver. Passing up such vague and unsupported statements as "stimulation of biological and fermentative processes of the liver", by insulin, we see that Bloch³ gave concrete evidence that insulin affects rearrangements of lipoid metabolism. He found that administration of insulin served to lower the abnormally high level of total lipoids in the blood of patients with diffuse hepatic disease and caused a sharp drop in ketone bodies lasting for two to three hours. At the end of this period the ketone bodies, especially beta-oxybutyric acid, returned to, or exceeded, the original high level. These phenomena which Bloch associated with an assumed increase in hepatic glycogen probably are due to the opposite process of increased glycogenolysis as indicated by our glycogen determinations. Such an interpretation is also favored by this author's own observations that administration of glucose had a similar but a more prolonged effect on the lipemia and ketosis of his patients. The ultimate increase of ketone bodies after insulin would according to this interpretation, be explained by a diminished output of glucose from the liver during the time necessary for a reaccumulation of glycogen up to the

amount characteristic of the functional equilibrium of the liver in a given patient.

Whatever the explanation the significant fact is that as regards the metabolism of fats glucose accomplishes at least as much as insulin. In addition it is known from clinical observations that administration of glucose reduces prolonged coagulation time in jaundice¹⁵ and exercises a protective action against delayed chloroform poisoning.

On the experimental side it has been shown that injections of glucose prolong the lives of animals in induced uremia and diminish the severity of lesions caused by intraperitoneal administration of trypsin, by photodynamic injury, and by a number of hepatic poisons.²⁴ Finally, Ravdin demonstrated increased regeneration of hepatic parenchyma due to glucose in animals with obstructive jaundice after release of the ligature of the common bile duct.

In this connection it may well be asked whether the reported beneficial effects of the insulin-glucose therapy in diseases of the liver are not accomplished by glucose and perhaps in spite of insulin. At any rate the present experimental and clinical evidence does not warrant the use of insulin in hepatic diseases unless there is a co-existent diabetes mellitus.

SUMMARY

1. In normal animals fed glucose the injection of insulin decreases the amount of glycogen deposited in the liver. The relative increase in hepatic glycogen is inversely proportional to that at the beginning of the experiment and in animals with a high initial glycogen content of the liver the

does not hinder accumulation of this substance as seen from the experiments with fasting and with thyroxin medication

The probable explanation of the decrease in glycogen of the damaged liver lies in the fact emphasized by Macleod²¹ that insulin in non-diabetic animals "distorts the whole of metabolism by overstimulating certain phases of it. The excess causes some parts of the metabolic machinery to go too quickly or too slowly for other parts upon which it has no influence. Such disorganization may lead to the accumulation of intermediary products of metabolism having a detrimental influence on the working of the machine as a whole." Such a disturbance of the metabolic equilibrium would be even more marked in animals with injury of the liver. In these animals the insufficiency of hepatic parenchyma is evidently such that they fail to compensate for greater glycogenolysis due to insulin by increased glycogenogenesis in spite of an excess of glucose in the blood.

That the liver under the conditions of our experiments still retains its power of glycogenogenesis is shown by the presence of some hepatic glycogen in every examined animal. To this can be added an increase in hepatic glycogen after administration of glucose without insulin in rabbits subjected to chronic phosphorus poisoning.

In rabbits convalescing from chloroform poisoning the glycogen content of the liver was still low in spite of a practically complete structural regeneration and a normal response to the modified glucose tolerance and epinephrin tests. In addition after insulin and glucose there was a de-

crease in hepatic glycogen which, however, did not exceed the limit of experimental error, and therefore can be considered only as indicating that there was no rise in glycogen content. Thus, the first abnormality of carbohydrate metabolism to disappear during convalescence from chloroform poisoning, is explained by the work of Doljansk²² with cultures of hepatic tissue. This author showed that active proliferation of hepatic cells *in vitro* is antagonistic to glycogen accumulation, but that these cells could be made to fill with glycogen by artificially slowing their growth. The same is evidently true of a rapidly regenerating liver *in vivo*.

THE PLACE OF INSULIN IN THE THERAPY OF HEPATIC DISEASES

Having seen that insulin reduces the deposition of glycogen in the liver of normal animals and actually decreases the already small original amount of glycogen in the experimentally damaged liver in spite of administration of glucose, we are confronted with the question to what extent this knowledge can be applied to hepatic diseases in man. In answering this question two considerations are of importance. The first is the essentially uniform character of hepatic injury whether induced in experimental animals or spontaneously occurring in human beings. This conception, as discussed elsewhere,²³ is supported by microscopic evidence and by observations on the metabolic activity of the liver.

The second consideration is the similarity between the lesions of phosphorus and of delayed chloroform poisoning on one side, and subacute

yellow atrophy and catarrhal jaundice on the other. Incidentally it is in the last two diseases that the insulin-glucose therapy is being particularly advocated. For these reasons it is felt that the obtained data on the behavior of glycogen in experimentally injured livers have a bearing on diseases of the liver in man.

Let us turn now from the subject of hepatic glycogen to other evidence in favor of a beneficial action of insulin in diseases of the liver. Passing up such vague and unsupported statements as "stimulation of biological and fermentative processes of the liver", by insulin, we see that Bloch³ gave concrete evidence that insulin affects derangements of lipid metabolism. He found that administration of insulin served to lower the abnormally high level of total lipoids in the blood of patients with diffuse hepatic disease and caused a sharp drop in ketone bodies lasting for two to three hours. At the end of this period the ketone bodies, especially beta-oxybutyric acid, returned to, or exceeded, the original high level. These phenomena which Bloch associated with an assumed increase in hepatic glycogen probably are due to the opposite process of increased glycogenolysis as indicated by our glycogen determinations. Such an interpretation is also favored by this author's own observations that administration of glucose had a similar but a more prolonged effect on the lipemia and ketosis of his patients. The ultimate increase of ketone bodies after insulin would, according to this interpretation, be explained by a diminished output of glucose from the liver during the time necessary for a reaccumulation of glycogen up to the

amount characteristic of the functional equilibrium of the liver in a given patient.

Whatever the explanation the significant fact is that as regards the metabolism of fats glucose accomplishes at least as much as insulin. In addition it is known from clinical observations that administration of glucose reduces prolonged coagulation time in jaundice¹⁵ and exercises a protective action against delayed chloroform poisoning.

On the experimental side it has been shown that injections of glucose prolong the lives of animals in induced uremia and diminish the severity of lesions caused by intraperitoneal administration of trypsin, by photodynamic injury, and by a number of hepatic poisons.²⁴ Finally, Ravdin demonstrated increased regeneration of hepatic parenchyma due to glucose in animals with obstructive jaundice after release of the ligature of the common bile duct.

In this connection it may well be asked whether the reported beneficial effects of the insulin-glucose therapy in diseases of the liver are not accomplished by glucose and perhaps in spite of insulin. At any rate the present experimental and clinical evidence does not warrant the use of insulin in hepatic diseases unless there is a co-existent diabetes mellitus.

SUMMARY

1. In normal animals fed glucose the injection of insulin decreases the amount of glycogen deposited in the liver. The relative increase in hepatic glycogen is inversely proportional to that at the beginning of the experiment, and in animals with a relatively low glycogen content of the liver the effect

diminution of this substance may result

2 In rabbits with experimentally damaged livers the glycogen content of the liver is low. The addition of in-

sulin to administration of glucose in these animals causes a further decrease in hepatic glycogen

3. Insulin medication is not indicated in decrease of the liver

REFERENCES

- ¹UMBER, F. Akute, subakute und chronische Leberatrophie, Handb d med, 1926, iii, J Springer, Berlin, p 77
- ²KIMURA. Ein weiterer Fall von subakuter gelber Leberatrophie mit vorgeschrittener Regeneration mit besonderer Berücksichtigung des Glykogenschlusses, Beitr z path Anat u z allg Path, 1914, lvi, 211-236
- ³BROCH, I. Untersuchungen über den intermediären Fettstoffwechsel bei diffusen Leberparenchymläsionen unter Insulin-Kohlhydratwirkung, Klin Wchnschr, 1931, x, 937
- ⁴ALTHAUSEN, T. L., and THOMAS, F. The influence on carbohydrate metabolism of experimentally induced hepatic changes, I, II, and III, Arch Int Med, (in press)
- ⁵RICHTER, P. F. Über Insulinbehandlung hepatargischer Zustände, Med Klin, 1924, xx, 1381-1382
- ⁶JACOBY, H. Die Insulin-Zucker-Behandlung der Leberinsuffizienz, Deutsch med Wchnschr, 1926, lii, 64
- ⁷GRUNFENBERG, K. Über die Wiederherstellung geschädigter äusserer Organfunktion von Leber und Pankreas durch die kombinierte Insulin-Traubenzucker Therapie, Deutsch med Wchnschr, 1926, lii, 271-272
- ⁸SCHNEIDER, H. Über die Behandlung des Icterus catarrhalis mit Insulin, Wien klin Wchnschr, 1926, xxxix, 1277-1278
- ⁹VON JAKSCH-WARTENHORST. Insulin und Nichtdiabetiker, Munch med Wchnschr, 1926, lxxiii, 1565-1567
- ¹⁰Reference 1, p 90
- ¹¹KLEIN, O., and HOLZER, H. Zur Insulinwirkung bei Leberkranken, Klin Wchnschr, 1927, vi, 157-158
- ¹²BAMBERGER, J. Zur Insulinbehandlung hepatargischer Zustände, Deutsch med Wchnschr, 1927, liii, 1690-1692
- ¹³DREYFUS, C. Les progres recents de la thérapeutique des affections pericholiques du foie. Paris med, 1928, i, 459-458
- ¹⁴GALANTER, M. A. P., and SWANWASS, H. L. Observations cliniques sur le traitement métabolique de des affections parenchymateuses du foie, Arch d med de l'app digestif, 1930, xx, 1070
- ¹⁵RWYLL, I. S. Some aspects of carbohydrate metabolism in hepatic disease, Jr. Am Med Assoc, 1929, xciii 1193-1197
- ¹⁶MACLION, J. J. R. Insulin, Physiol Rev, 1921, iv, 21-68
- ¹⁷CORLI, C. F. and CORLI, G. T. The fate of sugar in the animal body. VIII. The influence of insulin on the utilization of glucose, fructose and dihydroxyacetone, Jr Biol Chem, 1928, lxxvi, 755-795.
- ¹⁸RIMINO, P., VARLEY, B., and COLLAZO, J. A. Vergleichende Versuche über die Wirkung des Insulins und des Sinalbims auf die Glycogenmenge der Leber und des Muskels, Klin Wchnschr, 1928, vii 2186-2190
- ¹⁹CORLI, G. F., and CORLI, G. T. The influence of insulin and epinephrine on glycogen formation in the liver, Jr, Biol Chem, 1929, lxxxv, 275-280
- ²⁰VON NOORDEN, C. H., and ISAAC, S. Die Zuckerkrankheit und ihre Behandlung, 1927, J. Springer, Berlin, p 33
- ²¹MACLION, J. J. R. Lectures on the physiology of glycogen and the rôle of insulin and epinephrine in carbohydrate metabolism, Lancet, 1929, ii, 55-60
- ²²DOLJANSKI, L. Le glycogène dans les cultures de foie, Compt rend Soc. de biol, 1930, cv, 504-506
- ²³ALTHAUSEN, T. L. Etiology and pathogenesis of hepatic cirrhosis, (to be published shortly)
- ²⁴PREITZER, H., and STANDLNATH, F. Zur Kenntnis der Traubenzuckerwirkung bei Eiweissberfallsvergiftungen, Klin Wchnschr, 1925, iv, 119

The Pituitary and the Sugar Tolerance Curve*

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THE history of the relation of a disturbance in sugar metabolism to pituitary disease may be divided into two epochs, that prior to 1911, when rough, more or less scientific observations showed glycosuria with and without the administration of sugar in one group, and the inability, in another group, to produce glycosuria after the administration of sugar, and that epoch since 1911 when Goetsch, Cushing and Jacobson showed that sugar tolerance is increased in hypopituitarism, as determined by blood sugar determinations. From that date down to the present, numerous workers have verified that observation, and in various ways have applied it to the diagnosis of hypopituitarism, in the form of the so-called sugar tolerance curve. With the advent of insulin, and the demonstration of the opposed action between the posterior pituitary hormone and insulin, further evidence of this was shown (Burn).

The introduction of the sugar tolerance curve determination heralded a means of measuring this previously noted increase or decrease in sugar tolerance, but the lack of standardization of the procedure, and other affecting measures, has led to a series of results varying from one extreme to the other. On the one hand, John said "the increase in tolerance in hypopituitarism is characteristic, almost a straight line", and Hale-White and Payne wrote that "since most definite

cases of pituitary lesions tend to have an abnormal curve, the finding of a normal curve, may be considered to weigh against there being any abnormality of the pituitary functions". On the other hand, Engelbach, though having tried the application of a sugar tolerance curve determination, discontinued its use, and recently Glassberg wrote "I am unable to find any one curve which may be considered diagnostic of any of the conditions under consideration (endocrinopathies including hypopituitarism)", and further "I feel that the sugar tolerance curve as we have used it as a routine up to this time yields no information of diagnostic value in differentiation of normal and endocrinopathic conditions". Such extremely divergent conclusions demand scrutiny, study and explanation.

There are a great number of factors which influence the level of the blood sugar in an individual at any given time, and these factors may vary from day to day. The coexistence of a hidden lesion or lesions, with the apparent or suspected lesion, may greatly affect the sugar level, both before and after glucose ingestion—thus disturbances of the liver, pancreas, thyroid, changes in diet, disturbed gastrointestinal function, previous starvation or "dieting," excitement and medications. Thus "tolerance curves" repeated in a patient at an interval of even several days may not be identical. The amount of liquids and food taken prior to the test exert an influ-

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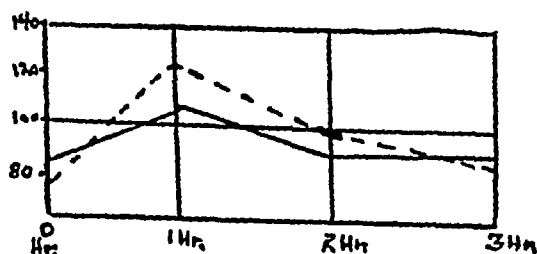
pain concurrent with venous puncture (especially when repeated failures are encountered), and numerous other factors, many non-apparent and not realized, all can modify the curve, in the same individual, and although John argues that the differences in the weight of the patient and the amount of glucose taken make but little difference in the curve, and the various observers use from 25 to 100 grams of glucose, some, on a fasting status, and others on *any* previous meal, with no definite time interval, we will attempt to show that the curves will vary greatly, with the variations in the amount of glucose, fasting, or food partaken.

Thus the same patient, under identical standardized conditions, (as described later), with a different amount of glucose, after a 48 hour interval showed the following differences

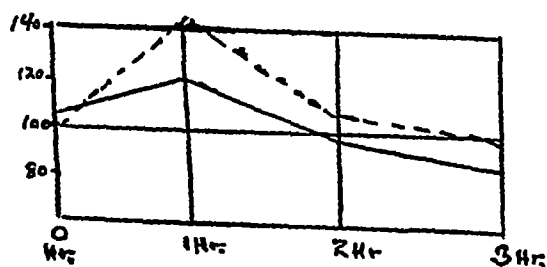
50 grams — 150 grams ----

Mgs. Sugar

Case 1



Case 2



Case 3

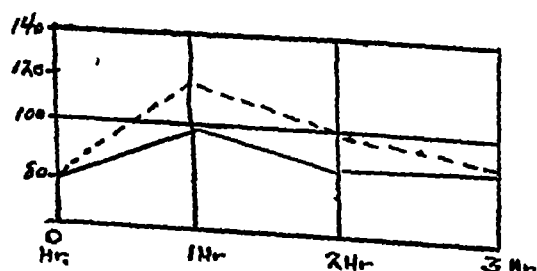


FIG 1

Compare the curves in a case of definite hypopituitarism in a boy (Lorain type of infantilism), given first 175 gram of glucose per kilogram of body weight, on 1 April, later 150 grams of glucose, one week later.

52.5 gram glucose, i.e., 175 grams per 1000 body weight, body weight 30 kbm (Curve —). 150 gram glucose (Curve ----).

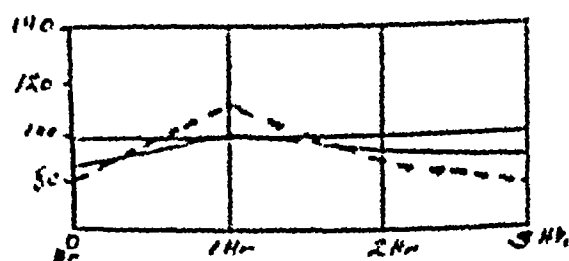


FIG 2

The first curve (—) is that of increased tolerance, while the second curve (----) is, to all intents and purposes, normal.

Note the difference below, in another case, figure 3, in the curve following a 48 hour fast (----), and the non-fasting curve with the same amount of glucose, 175 grams per kgm of body weight, (—), in the same patient, repeated after ten days.

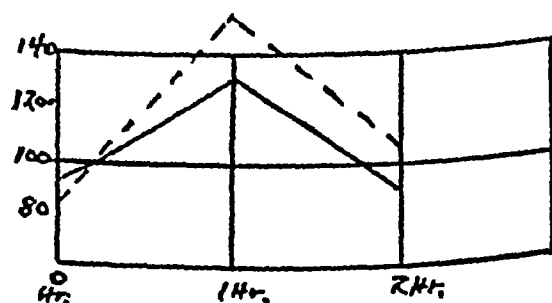


FIG 3

Two hours before the curve (—) determination, a meal consisting of four slices of bread, dish of ice-cream,

one pastry and coffee, with two lumps sugar was given. After a study of this phase of the subject, Myers sums it up "it is well known that the tolerance for glucose is lower in the fasting condition than after glucose has been given, apparently as a result of its stimulus to the glycogen forming mechanism, due possibly to the liberation of insulin by the pancreas. At the end of three hours this initial stimulus still appears to be sufficient to enable the normal organism to readily handle the amount of glucose given without undue hyperglycemia." The importance of the so-called standard breakfast, as later described, is thus emphasized.

Further, the blood sugar curve varies with another factor—whether so-called capillary blood (obtained by finger puncture) or venous blood is used. Note the two curves below by Foster. Foster pointed out that the blood obtained by finger puncture is virtually arterial blood. "He has found that although the sugar concentration of venous and finger (also arterial) blood is the same in the fasting state, after the ingestion of glucose there is a more rapid and greater rise in the finger blood than in venous blood." To quote Myers further, who sums up the work of Foster in this regard "the logical explanation for this would appear to be found in glycogen formation in the muscle tissue, since the muscle stands between the arterial and venous blood. It is also apparent that when this glycogen synthesis has once been started it carries the sugar of the blood below the initial level as a result of overactivity of the glycogen forming mechanism."

Glucose curves—simultaneous ven-

ous and finger blood (Foster) Venous blood (—) Finger blood (----). Amount of glucose, 100 gm

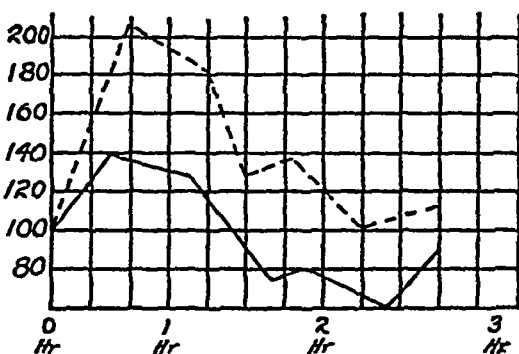


FIG 4

In 1925 we showed that repeated injections of milk produced an increase in the sugar tolerance. Wood-yatt claims that some drugs such as phosphorus and arsenic may cause glycosuria by causing an increased glycogenolysis.

Therefore, to perform the test properly, and to properly evaluate the curve produced, the effect of the administration of various diets, drugs, injections, treatments, etc., must be kept in mind. It is then apparent that discrepancies in the curves repeated in the same individuals, with the same diagnosis, can be expected, depending on

- (1) Type of blood used for the sugar determinations.
- (2) Time of day the test is performed.
- (3) Time of the previous meal.
- (4) Nature and amount of the previous meal.
- (5) Degree of pain, anxiety, excitement and mental status of patient.
- (6) Dieting and treatment of patient for the days and weeks leading up to the test.

- (7) Amount of the fluid taken with or before the glucose.
- (8) Amount of glucose taken and its dilution.
- (9) Presence or absence of other co-existing pathology or lesions besides the suspected condition.
- (10) Individual peculiarities in rate of absorption, glycogenesis, rate of hormone manufacture, etc

For these reasons we have followed the method of Kilhan, as standardized in the laboratories of the New York Post Graduate Medical School and Hospital Without any change in diet and habits, and prior to any medication (especially thyroid, thyroxin, insulin, antuitrin, pituitrin, foreign proteins parenterally, etc) the patient reports for his curve determination two hours after his breakfast which consisted of two slices of bread, one egg, and a cup of tea or coffee He is first given a drink of water, the amount equal to that which will be used to make the glucose a 50 per cent solution, and he empties his bladder One hour later, he voids again, and a specimen of venous blood is taken He then immediately takes the glucose, 175 grams per kilogram of body weight in 50 per cent solution Specimens of blood (and urine) are taken hourly for two, three and four hours It is true that by taking only the hourly specimens the highest point may be overlooked, but for practical purposes it suffices

Curves regarded as examples of normal tolerance

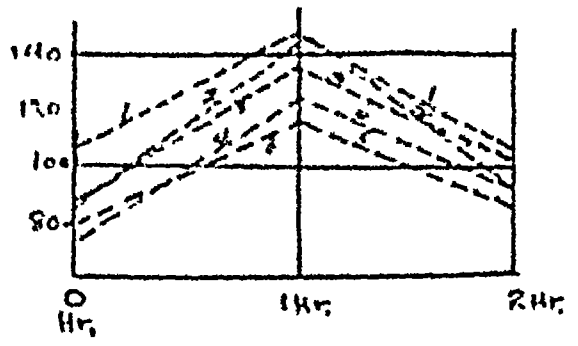


FIG. 5

From studying numerous such curves regarded as normal, we have reached the rough rule that the level at the first hour is approximately from 40 per cent to (60) per cent above the 0 hour with a tendency to return to about the 0 hour level at the end of the second hour.

We will confine ourselves at this time to more or less positive cases of hypopituitarism, without other complicating conditions, where the stigmata and clinical findings were well marked It has been our clinical conception from some years of observation that hypopituitarism does occur without obesity (as shown in the laboratory on animals by Smith), and can also occur without much change in the sugar curve. However it is our impression that the sugar curve deviation from the normal in uncomplicated hypopituitarism is a rough measure of the degree of hypofunction

Below are some illustrative data in a number of marked cases of hypopituitarism.

AGE	SEX	SELLA TURCICA	0 HR BL. SUGAR	1 HR BL. SUGAR	2 HR BL. SUGAR
14	M	50% undersize			
20	F	Congenitally small, clinoid processes almost completely bridged	82	90	87
18	F	50% undersize, with suprasellar shadow suggesting tumor	78	80	76
30	M	Large sella turcica, marked erosions	80 92	76 95	75 90

The curves in these cases approximate the flat curve, plateau or straight line described by John and others. Below are some illustrative data in a number of suspected or mild cases of hypopituitarism. We have seen a great number of such but have picked only a few to make this point clear.

0 HR	1ST HR.	2ND HR
162	305	294

She received intensive and continued x-ray therapy. Insulin and diet seemed to be of little value, and were soon discontinued. One year later her sugar curve was as follows —

0 HR	1ST HR	2ND HR
93	121	107

Clinically she has gained about 30 pounds,

AGE	SEX	SELLA TURCICA	0 Hr	1 Hr	2 Hr.
25	F	1/3 undersize	92	115	101
30	F	Congenitally small	102	130	110
27	M	Negative	85	116	91
26	M	Congenitally small	96	114	93

It will be noted that here we had an elevation after glucose administration varying from 25 per cent to 37 per cent, as compared to the 40 per cent to 60 per cent rise in the normals.

The opposite syndrome—hyperfunction—may therefore give a decreased sugar tolerance, with the corresponding curve, such probably occurring in the so-called acromegalias with diabetes. These, because of treatment, x-ray or surgery, or because of a “natural burning out process” may gradually obtain an increase in their sugar tolerance, and as the original process regresses, or because of x-ray or surgery, may finally develop, as an end picture, the “flat curve” shown above, indicating, perhaps as an end picture, hypofunction.

The following case demonstrates this point. A lady, aged forty-five years gave a history of headaches of ten years duration, gradually increasing in frequency and severity, and lately noticed that her features were becoming heavier and her hands and feet larger. At this time the visual field determination showed a marked temporal constriction, and x-ray of the skull revealed a large sella turcica. Soon she began to have itching, thirst, polyuria and lost 20 pounds. Her sugar curve at this time was as follows —

her headaches have practically ceased, her visual fields are markedly improved, and she has become somewhat obese, lethargic and slow. With the advent of a clinical syndrome, suggesting pituitary deficiency, the sugar tolerance has swung from the extreme suggesting the diabetic curve to the other extreme, the flat curve of hypopituitarism. The reader is referred to the writings of Colwell, Allen, Lesser, and others for such similar experiences, data and impressions.

In cases of hypopituitarism (non-tumor cases with small sella turcicas, obesity, etc.), having observed a number over a period of years (fifteen such cases having been followed about eight years), we could see the changes in the sugar tolerance curve, paralleling the improvement. Below are examples of this.

	0 HR	1ST HR	2ND HR
Case 1 (1923)	94	98	90
(1926)	87	110	92
(1930)	89	121	94
Case 2 (1925)	82	87	85
(1928)	90	111	96
(1930)	88	117	85

Gardner, Hill, Jones and Smith observed, too, that “with improvement the sugar tolerance curve approaches the normal.”

CONCLUSIONS

From the data, observations, and literature we find the following conclusions justified:

1 Certain pituitary hormones have an action on sugar tolerance, in some respects, diametrically opposed to the action of insulin.

2 The administration of glucose to an individual will produce a curve, if the blood sugar levels following this administration are plotted

3. The random administration of glucose—fixed amount of glucose for all patients regardless of size, fasting state, etc.—produces so variable a curve that its value in diagnosis under these conditions is nil

4 Capillary blood curves are not

identical with venous blood curves and should be discarded for curve determinations.

5 To be properly performed the method described should be followed, or some better method not yet devised

6 When thus carried out, other things being excluded, e.g., medications, diseases, etc., deficiency is frequently characterized by an increased tolerance, the degree of tolerance increase being a rough measure of the degree of deficiency

7. Pituitary hyperfunction is often associated with a decreased sugar tolerance resembling diabetes mellitus, but amenable in some cases to improvement, as the hyperfunction is controlled.

BIBLIOGRAPHY

- GOETSCH, E, CUSHING, H, and JACOBSON, C Carbohydrate tolerance and the posterior lobe of the hypophysis cerebri an experimental and clinical study, Johns Hopkins Hosp Bull, 1911, xxii, 165-190
- BURN, J H Modification of action of insulin by pituitary extract and other substances, Jr Physiol, 1923, lvi, 318-329
- JOHN, J H A study of 1100 glucose tolerance tests, Med Jr. and Rec, 1930, cxxxi, 287.
- HALE-WHITE, R, and PAYNE, W W Diagnostic value of dextrose-tolerance curves, Quart Jr Med, 1927, xx, 457-469
- ENGELBACH, W Personal communication
- GLASSBERG, B Y The diagnostic value of the sugar-tolerance curve in endocrinopathies, Arch Int Med, 1930, xli, 984-987
- MYERS, V C Practical chemical analysis of blood, 1924, C V. Mosby Company, St. Louis, Mo., 87-90
- FOSTER, G L Studies on carbohydrate metabolism, Jr Biol Chem, 1925, lv, 291-301.
- EIDENBERG, J Milk parenterally in arthritis, Med Jr. and Rec, 1925, cxxi, 674-676
- WOODHART, R T Quoted in Wells, H G, Chemical Pathology, 1914, W B Saunders Company, Philadelphia, 573
- SMITH, P E Hypophysectomy and replacement therapy in rat, Am Jr. Anat, 1930, xlv, 205-273
- COLWELL, A R Relation of hypophysis to diabetes mellitus, Med, 1927, vi, 1-39
- ALLEN, R E, and LISSER, H Roentgen ray therapy of hypophysis in patient with acromegaly, its effect on dextrose-tolerance, Arch Int Med, 1928, xlii, 703-707.
- GARDNER-HILL, H, JONES, I, and SMITH, J F Pituitary obesity in adolescence, Quart Jr Med, 1925, xviii, 309-320

Clinical Interpretation of Jaundice Based on Physiologic Principles*†

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THE tremendous value in diagnosis of bed-side approach, based on a large clinical experience is known to all. In many disease states, this suffices, and memory of characteristic symptoms, physical findings and laboratory data makes accurate diagnosis possible. The problem is not so simple in diseases associated with jaundice, a leading symptom that all may recognize easily, but which is due to so many conditions, intra- and extra-hepatic, that extreme difficulty often arises in interpretation. Here, experience alone, plus the most exact functional tests known, fails to lead to exact diagnosis in a vast number of cases. Notwithstanding painstaking reasoning and analysis, one must often admit doubt at the bedside, and defeat in the operating room or at the autopsy table. The difficulties presented prompt an attempt to create further clinical order, building upon a foundation of underlying physiologic and pathologic principles.

Jaundice is a leading objective symptom, a staining of the plasma and of the tissues, consequent upon increase in the bilirubin content, at the site of

discoloration, local or general. The tissues of the body, however, do not stain equally, some actually remaining free of pigment, no matter what the intensity of general coloration. Most highly colored are the blood vessels and heart valves, the skin, mucous and serous membranes, kidneys, lungs, spleen and liver. Cartilage, the cornea, and the cerebrospinal system (brain and spinal cord) retain their normal appearance. (A single exception here is the staining of the infundibulum cerebri in some cases of icterus neonatorum gravis.) It is also interesting to note that pure secretions, exemplified by the salivary and gastric juices, and the cerebrospinal fluid, are free of bilirubin. Excretions, as urine and perspiration are however, deeply stained.

Numerous attempts have been made to explain this inequality of tissue staining. The facts certainly oppose acceptance of the "imbibition" theory, with its claim for general tissue absorption of the bile pigments from the circulating fluids. If this mechanism was operative, one should expect an equal staining throughout. Rose and his associates attempted to answer this question. His experimental work indicates the importance of elastin, the associated secretion of elastic tissue, as a factor in the

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chemical substance, attracting bilirubin. Those tissues rich in elastin stain deeply, those without elastin are free of pigment. Adipose tissue containing no elastic tissue appears intensely colored, only because of the small amount of pigment needed to contrast with the pure white of the fat. This color, too, can be washed off easily, which is not true of the other tissues. Elastin, *in vitro*, added to non-stainable tissues appeared to alter the response to the pigment. This chemical affinity conception also fails of complete satisfaction. It seems likely to us that the staining of a specific tissue is related also to the function of that particular tissue as regards bilirubin pigment — formative and excretory. It is most concentrated at sites of its formation in the reticulo-endothelial system (*vide* below), principally spleen, liver and bone-marrow, and also marked in organs of its normal and abnormal excretion — kidney, skin and intestines.

Here, one must pause momentarily to inspect the evidence concerning the nature, formation and excretion of bilirubin and its associated pigments.

Virchow² found crystals in extravasated blood, strongly resembling bilirubin. Knowing that they came from the hemoglobin of the red cell, though unable to furnish chemical proof of their identity, he named the substance hematoïdin. The proof that this substance was bilirubin subsequently was furnished by Jaffé, Fischer, and Bumstead and Rich. The possibility has been suggested that bilirubin also may be formed from pigments other than blood hemoglobin. Myohemoglobin may contribute very slightly (Whipple, Hooper and Robschert-Robbins). The

importance of chlorophyll,³ and its associated pigment is denied (Bollman, Sheard and Mann). The only justifiable conclusion seems to involve blood hemoglobin as practically the sole source of supply for bilirubin formation.

Prior to Virchow, the conception prevailed that the production of bilirubin occurred exclusively in the epithelial cells of the liver. The great pathologist's finding was the first bit of evidence indicating the possibility of extra-hepatic formation. However, it did not attract its deserved attention for many years. The work of Minkowski and Naunyn⁴ (1886) also appeared to corroborate the longstanding belief. Their inability to produce jaundice in hepatectomized geese with hemolytic agents, as arsenureted hydrogen, led them to the dictum "without liver, no jaundice". Several years later (1889) Lowitt,⁴ producing hemolysis in the blood of frogs, found red cell debris, hemoglobin, bile pigment and an iron residue, in the Kupffer cells of the liver. He indicated that bile pigment could be formed outside the liver epithelial cell, but did not deny the latter's activity in this regard. In 1912, McNee,⁵ in the laboratory of Aschoff, repeated the experiments of Minkowski and Naunyn with identical results, but now, with a new interpretation. He ascribed the absence of jaundice to the absence of the Kupffer stellate cells, so large a portion of the reticulo-endothelial system in geese. The conception of this system had been formulated recently by the Aschoff school and McNee was first to attract attention to it in connection with bilirubin formation. The other

members of the reticulo-endothelial system are the cells lining the sinuses of the spleen, the endothelium of the lymph and blood vessels, the capillaries of the bone-marrow, the serosae, the endothelium of the suprarenals, omentum, lungs, hypophysis and the macrophages of the blood

Credit goes to Whipple and Hooper⁶ for stimulating the important researches which yielded the conclusive evidence. Their deductions, however, derived from producing jaundice in animals whose livers supposedly were excluded from the circulation, were challenged. Rich,⁷ Makino⁸ and others denied that the liver had been excluded completely enough. Mann⁹ and his co-workers, in their series of ingenious experiments, then successfully dehepatized dogs and were able to produce an icteric state with hemolytic substances. Immediate universal confirmation followed. Rich succeeded in producing jaundice following complete abdominal evisceration. The contrary findings of Rosenthal, Melchior and Licht,¹⁰ of the Minkowski school, who failed to produce jaundice in hepatectomized dogs, after injecting such substances as toluylenediamine, were largely vitiated by such work as that of Joannovics and Pick.¹¹ The latter's experiments indicated that the substances used were toxic to the liver cell, and thus could not produce icterus in the absence of the liver. A mechanism therefore appeared to exist, outside the liver, which could assume the function of bilirubin formation.

Much evidence points toward the cells of the reticulo-endothelial system as active in this extra-hepatic formation of bilirubin. Kodama,¹² in experi-

mental icterus, showed bile pigment in the Kupffer stellate cells before it could be found in the epithelial cells of the liver, and before it reached the serum. In mechanical icterus, the Kupffer cells contained much more of the pigment. Haldemann¹³ demonstrated marked deposition of pigment in the reticulo-endothelial cells of the bonemarrow, after injecting laked blood intravenously. Several groups (Mann,⁹ Ernst and Szappanyos,¹⁴ Komari and Iwao¹⁵) demonstrated increased formation of bilirubin in the spleen and bone-marrow after injecting hemoglobin into the blood flowing to these sites, and in the perfused spleen. Lepehne,¹⁶ and Eppinger¹⁷ believed their attempts at blocking the reticulo-endothelial system with substances such as collargol resulted in the diminished activity in this process of bile pigment formation. Rich, in tissue culture studies, noted that only mesodermal cells were able to transform hemoglobin into bilirubin, and this intracellularly, possibly with the aid of an hydrolytic ferment.

Evidence certainly indicates that the cells of the reticulo-endothelial system are able to manufacture bile pigment under the abnormal conditions of the various experiments performed. Whether this is the only method adopted by the body in health and what proportion of the work is performed by the various members are questions still to be answered. It is unlikely as Mann first indicated that the reticulo-endothelial elements of the spleen and bonemarrow are exclusively concerned in the extra-hepatic formation. These deductions are in accord with dehepated animals which develop

transferable to the intact animal, with its liver and Kupffer cells *in situ*. His more recent work indicates that in the absence of liver and spleen, the rate of production remains normal, presumably due to bonemarrow activity. Certainly, the ability of reticulo-endothelial cells everywhere to form bilirubin is attested by numerous clinical instances—regional icterus (Umber and Rosenberg), jaundice associated with pulmonary intarction, that following intra-peritoneal hemorrhage, etc. From analysis of the evidence presented, the reticulo-endothelial cells of the liver, spleen and bone-marrow appear to be the normal agents for bilirubin production, with the remainder of the system also capable of so functioning under more abnormal conditions.

The following facts, however, seem established with a high degree of assurance (1) That bilirubin is formed practically entirely from the hemoglobin of broken-down red blood cells; (2) that the cellular elements of the reticulo-endothelial system are probably active in this transformation; and (3) that the epithelial cells of the liver merely excrete the pigment into the biliary radicles which convey it to the gallbladder and intestines. It is evident, therefore, that alterations in the bilirubin content of the serum, and thus the tissues, may result from single or multiple derangements anywhere along this chain of bilirubin formation and excretion. Jaundice or the state of increased bilirubin concentration therefore may be due to (1) an increased destruction of red blood cells, and overactivity of the reticulo-endothelial system (2) disease of the hepatic epithelial cells, and consequent in-

complete or absolute failure of removal of bilirubin from the blood, and incomplete propulsion into the biliary radicles, and (3) blockage of the excretory channels after proper elimination by the hepatic cell.

Rich has contended recently that jaundice rarely, if ever, results from simple overproduction of bilirubin. It is his belief that the reserve power of the normal liver is so great that the organ can care adequately for any excess of bilirubin and invariably prevent the establishment of an icteric state. Disturbance of liver cell function is claimed always to co-exist. He ascribes great importance to atrophic changes in the epithelial cells about the efferent vein of the liver lobule, found in various anemic and infectious diseases. Experimentally, similar lesions have been produced, under conditions pointing toward anoxemia as the responsible factor. Although this work is highly informing and leading, it is questioned whether the facts presented warrant the entire clinical conclusion. It would seem that Rich is ascribing too great an importance to pathology, usually minor. It is likely that in chronic cases of "hemolytic" icterus that have persisted for an extended period, the degree of liver dysfunction may proceed to clinical significance. The usual case, with hemolysis of red cells the crux of the clinical picture, does not appear to require such preceding damage. Although it is true that jaundice of any marked intensity practically always has an hepatic element, icteric states of milder degree, though with definite hyperbilirubinemia and tissue staining, appear to result independent of such affection. The

increased production of bilirubin on red cell destruction may be conceived as an actual compensatory mechanism, a pigment being formed from the liberated hemoglobin which is tolerated well by the tissues, and a colorless iron-containing compound being split off which can be stored and utilized again.

It is upon the foregoing facts that our modern classifications of icterus are based. McNee¹⁸ called the first group, "hemolytic", the second class, "hepatocellular" or "toxic" and the third "obstructive". Although it is true that all three terms do not possess identical connotations (hemolytic and obstructive, pathogenesis, and toxic, etiologic) this grouping is simple, satisfactory, and adequate for clinical usage.

Recently, Stuber¹⁹ suggested changes in nomenclature, attempting to add to the functional descriptiveness of the terms previously employed. He referred to the hemolytic as the "superfunction" group, since here mere overproduction of bilirubin leads to its increase in the serum and tissues. Whether "superfunction" better typifies this group than "hemolytic" is questionable. The implication of blood destruction certainly is better given by the latter term, though "superfunction" is of value in indicating the overactivity of the reticulo-endothelial system. Where there is no evidence of actual hemolysis, as after hemorrhages (intraperitoneal, pulmonary), blood dyscrasias and reticulo-endotheliosis, the latter term would seem more desirable. The "hepatocellular" group to Stuber is known as the "retention type of icterus, since even the normal quantity of bilirubin produced is partially retained, the malfunctioning epithelial cell being un-

able to excrete it completely. The obstructive class is called the "resorption" group. Here, no overproduction of bilirubin is found, the liver cell can propel completely the pigment brought to it, but somewhere along the course of the bile ducts, obstruction is met, and damming back of bile takes place. The continuity of the bile canaliculi is destroyed, bile reaches the perivascular spaces and is resorbed into the blood capillaries.

Rich used similar terms in his suggested classification, though with somewhat different application. "Retention" was used for cases with indirect Van den Bergh reaction and acholuria, though with increase of urobilin in urine and feces. This group includes the various forms of "hemolytic" icterus and jaundice resulting from mild interference with functions of the epithelial cells of the liver—as by anoxemia. "Regurgitation" was applied to those cases with direct Van den Bergh reactions, bile in the urine, and little or no urobilin in the stools. This class contains the forms associated with necrosis of liver cells. This classification does not appear to attach sufficient importance to clinical symptoms, nor does it adequately segregate cases on the basis of their underlying causes. Thus jaundice due to acute yellow atrophy is so essentially different clinically from that following a common duct obstruction by calculus that regrouping is undesirable. The basis of division, i.e., using the Van den Bergh reaction is also undesirable since similar findings may exist in either group at some stage of the disease process.

It is important to appreciate that all the classifications in use are based on

and with sharp or absolute boundaries. This follows because the diseases causing jaundice are not static; they are dynamic and may regress, or, what concerns us more may show progress. A case belonging to one group becomes modified, as a result of active etiologic factors and complicating pathological changes, and may actually deceive so that cause and effect are not distinguishable. To exemplify the progression of a disease process, with its final possession of the characteristic qualities of two or more groups, one may utilize a case of congenital hemolytic icterus. Here, the primary defect lies in the red blood cell, with its increased fragility leading to increased destruction, and hence, over-production of bilirubin. The case clearly belongs to the hemolytic or superfunction group. With the excretion of a concentrated bile, the scene is set for the formation of bile thrombi or actual calculi of bilirubin or mixed type. These form and may cause variable grades of obstruction with its attendant symptoms and findings. Now, both the formation and excretion of bilirubin are disturbed. Furthermore, Rich²¹ has pointed out that in the later stages of the disease, actual damage to the liver cell follows upon the long standing anemia, and its associated lowgrade anoxemia. Thus, the hepatocellular element is added with its disturbance in transferring bilirubin from the vascular to the biliary radicles. So, we have traced, in one disease state, progressive disturbance along the entire course of bilirubin production and excretion. Of paramount importance, however, is the understanding that the primary defect originated in the red

blood cell and in case of destruction by the cell of the reticulo-endothelial system. It is on this basis that this condition is classified as "hemolytic" icterus, and with a yardstick of these standards other icteric states are sorted.

The nature and implications of the Van den Bergh reaction now concern us, to aid its better utilization in diagnosis. This test, dependent upon the response of serum or plasma to the diazo reagent, yields differences of diagnostic import. A direct reaction which follows promptly upon the admixture of the serum and reagent is obtained with bile and the blood in icteric states associated with biliary obstruction or liver cell damage. The indirect reaction which requires the addition of alcohol is found in hemolytic types of icterus. The biphasic reaction is intermediary. The question was raised whether the different reactions were related to an altered composition of the bilirubin after passage through the liver cell. Several physical and chemical differences suggested that this might be so, namely, that direct bilirubin is oxidized more readily (Van den Bergh, Andrews); that it is more easily absorbed by the protein precipitate on alcohol precipitation (Van den Bergh), that it does not pass into solution with chloroform (Grunnenberg), that it is dialyzable through a collodion membrane (Hoover and Blankenhorn), which fact is probably related to the presence of bile in the urine in cases of obstructive and hepatocellular icterus, and its absence in hemolytic icterus. Recent work indicates, however, that the "indirect bilirubin" may exist in the blood in combination with other substances Feigl

and Querner suggest a lipoid linkage, Adler and Strauss, a protein combination. Thannhauser and Andersen claim that the addition of bile salts and cholesterol to an indirect bilirubin serum changes the reaction to direct, Stuber makes similar claims for uric acid. Barron's²² informing work is of importance. He added to normal blood serum increasing amounts of sodium bilirubinate, giving direct Van den Bergh reactions. Up to 12 mgm per cent, an indirect reaction was obtained, at 16 mgm per cent, a biphasic reaction, above this amount, a direct reaction. He concludes that "some constituent of the serum has a tendency to absorb bilirubin and prevents the immediate coupling with diazonium salts". A direct reaction would be obtained, therefore, when the amount of bilirubin present in the blood exceeds the absorbing ability of the important substances (probably serum globulin—Adler and Strauss, Barron), or substances are present in the blood (bile acids, cholesterol, uric acid) in large amounts, which by their stronger absorbability, prevent the absorption of bilirubin. The latter is then able to react immediately with the diazo reagent.

An understanding of the metabolism of urobilin also is necessary for proper analysis of its alterations in icteric states. Urobilin is the reduction product of the action of bacteria on bilirubin in the intestine (von Muller, McMaster and Elman²³). Some is reabsorbed from the intestine and returned to the liver for future use in pigment formation, some reaches the general circulation and is excreted by the kidneys, traces being found normally

in the urine. In the urine, urobilinogen is rapidly oxidized to urobilin. The threshold of the liver for urobilin is limited, and in the presence of liver cell disturbance, even the normal quantity cannot be cared for, more passes into the blood, and thus more is excreted in the urine. An increased urinary excretion also can be effected by an increased destruction of erythrocytes, with its increased production and excretion of bilirubin into the intestine, and therefore increased production of urobilinogen. Certain limitations of the diagnostic value must be noted: namely the increase in most acute infections where there exists no reason to suspect liver damage, the diurnal variation, more being excreted in the afternoon than in the morning, the failure of the kidney of chronic glomerulo-nephritis to excrete it, even in the presence of liver disease. It is evident that an increase of urobilinogen or urobilin in the urine can be utilized diagnostically only in conjunction with other clinical symptoms. Absence of these pigments in icteric states is, however, much more significant, indicating failure of bile to reach the intestine.

In attempting to differentiate clinically the types of icterus, our understanding of the extra-hepatocellular formation of bilirubin stands us in good stead. Proper appreciation of the fact that icterus may exist independent of significant liver cell dysfunction leads us to utilize clinical data more efficiently. We are able to segregate the entire group of hemolytic or superfunction icterus from those related to disturbance in the hepatic epithelial cells and bile passages and to predict the course of the disease and the

with icterus traceable to improper excretion of bilirubin, associated symptoms always are present pointing toward the liver as the seat of damage. In fact, not infrequently the patient directs attention to the liver area, in telling his story, covering it often with his hand. In catarrhal icterus, the vague digestive disturbances preceding the onset of jaundice, and the enlarged liver point the way. In obstruction to the ducts, the pain usually present, the tendency to acholic stools, etc., indicate the site of disturbance. The presence of itching favors this group. The Van den Bergh reaction is direct or biphasic, bile is present in the urine; urobilin may or may not be present depending on the amount of bile which reaches the intestines. *In the group of hemolytic icterus, where jaundice follows upon increased bilirubin production and a mere quantitative difficulty of liver cell excretion, the icterus exists as a leading objective symptom. Any concomitant subjective complaints point entirely away from the liver toward the cause of the hemolysis and its effects.* This is probably related to the before-mentioned fact that bilirubin, being the normal product of hemoglobin breakdown, is so well tolerated by the tissues and their cellular elements. In the congenital and acquired hemolytic icterus, the anemia and its consequences are outstanding, in the course of severe infections, it is merely an additional symptom, with chemical poisons leading to hemolysis, signs point toward this cause. The Van den Bergh reaction is indirect, bile is absent from the urine, urobilinuria is marked.

Is it possible further to analyze the functioning of the reticulo-endothelial

system and lead to additional aids in diagnosis? Normally, as indicated before, the destruction of red blood cells and formation of pigment take place in the Kupffer cells of the liver and endothelial cells of the spleen and bone-marrow. The excretion of bilirubin via the hepatic epithelial cells keeps pace, maintaining a constant level in the blood. Abnormally, in icteric states, it is conceivable that the process of pigment production may proceed along normal or abnormal channels. In hepato-cellular and obstructive icterus, the bilirubin is still the product of members of the reticulo-endothelial system, normally engaged in the exercise of this function of pigment formation. In true hemolytic icterus, a mere overactivity of the normal agents is at fault. We must recognize, in addition, however, a sub-group of cases of "super-function" or "hemolytic" icterus, in which members of the reticulo-endothelial system, everywhere in the body, not engaged normally in this activity of bilirubin formation also assume this function (endothelium of the peritoneum, the lung, the skin).

Clinical facts appear to substantiate this differential conception. In hepato-cellular and obstructive icterus, days intervene between the onset of activity of the causative factors and the occurrence of visible jaundice. For example, in catarrhal icterus, a period of prodromal symptoms of from four to five days to a week or more is found before the onset of jaundice. In calculus obstruction of the common bile duct, a period of forty-eight hours or more intervenes before icterus appears, with the exception of patients in whom

cholecystectomy has been performed previously. In congenital hemolytic icterus one cannot always define the true time interval, but even here, following the so-called "crisis", a period of several days elapses between the onset of the pain and the appearance of the deeper jaundice. A definite interval is noted following the activity of hemolytic substances — chemical or bacterial. In all these conditions, after removal of the local or general causes, the jaundice persists for a shorter, or usually, longer period, related probably to the greater degree of hyperbilirubinemia and also the greater ease of penetration and tissue staining of the protein-free bilirubin compound. Consequently, the need exists for a more prolonged period of recession.

On the other hand, in icteric states consequent upon bilirubin-forming activity of portions of the reticulo-endothelial system, not so engaged normally, differences are noted. If an extravasation of blood is slight, only regional icterus may follow, as in the skin following trauma. If moderate, as in an hemorrhagic effusion in the peritoneal cavity, or a moderate pulmonary infarction, moderate icterus is present. If a severe hemorrhage occurs within the body, universal icterus may occur. In icterus neonatorum, various gradations of this process may be seen, from small patches of regional icterus to complete jaundice (one of the main elements in this affection being the breakdown of red blood cells and actual formation of bilirubin by the endothelium of the skin). In all, the appearance of increased bilirubin (and associated pigments), locally and generally, is noted soon after the oc-

currence of the accident, usually only hours intervening. The discoloration in the skin appears soon after trauma (conjunctival hemorrhages alone remaining red until absorbed). Following massive hemorrhages into the peritoneal cavity as in ruptured ectopic gestations, or following large or multiple pulmonary infarctions, within six to twelve hours, the patient may be subicteric. The icterus of rapid appearance also has the faculty of rapid clearance, being gone very soon after removal of the causative factors.

It is essential, too, to note that disturbance in the bilirubin-excretory power of the liver cell may be of clinical importance in conditions where there exists neither visible jaundice nor latent jaundice, as evidenced by slight increase in the blood content of bilirubin. Interference with this excretory power of the liver is effected much more easily than with its numerous metabolic activities. In acute liver disease, all functions may be disturbed, often out of proportion to the degree of evident damage. In chronic disease, as cirrhosis, with its brunt of mesenchymal damage, the parenchymal cell slowly adapts itself to the acting forces and evidences no disturbed function unless taxed or overburdened. Proof of a relatively isolated dysfunction of the liver cell may then be demonstrated by taxing the individual with ingested or injected bilirubin. Bergman,²⁴ Ellbott,²⁵ and recently Harrop and Barron²⁶ considered "the bilirubin excretory power of the liver" the most delicate for testing the functional capacity of this organ. Retention is found in pernicious and other severe

anemias, acute infections, postarsphenamine and catarrhal jaundice some months after clinical recovery— all indicative of mild interference with liver cell function

Although the bilirubin-excretory test does indicate some hepatic cell dysfunction, it must be appreciated that this sudden over-burdening of the liver cell with bilirubin by far over-exaggerates the method of occurrence of icterus within the body. The rôle played by the epithelial cell in the development of an "hemolytic" icteric state cannot be accurately inferred from the result of this test

It should be evident that the present conception of the physiologic principles underlying the formation of bilirubin and the causation of icterus has led us far from the old Minkowski-Naunyn dictum, "without liver, no jaundice". Extra-hepatic production of bilirubin makes possible the development of icteric states, by forces acting entirely or mainly outside the liver. The importance to be ascribed to associated changes in the liver cells, as found by Rich, is still not definite. Certainly, they may aid in the progress of jaundiced states, but whether they are present, or needed, at its inception is questionable. Clinically, as indicated, one is justified in separating entirely, those groups of icterus due to causes, active intra- or extra-hepatically. The

presence in the former of associated symptoms indicating liver disturbance and the absence in the latter of any subjective complaints pointing toward such dysfunction are facts of important diagnostic value.

Summary

1 Jaundice as a leading objective symptom, when due to over-production of bilirubin exists free of any complaints pointing toward liver dysfunction. Any associated symptoms or signs reflect the cause of the hemolysis and its effects.

2 When jaundice follows disturbed function of the hepatic epithelial cell or obstruction of biliary ducts, signs point toward the liver as the seat of damage

3 It is suggested that the group of "hemolytic" or "superfunction" icterus may be divided clinically, dependent on whether the abnormal quantity of bilirubin is the product of members of the reticulo-endothelial system normally engaged in this production (liver, spleen, bone-marrow) or abnormally so functioning (endothelium of skin, peritoneum, lung, etc.)

4 The bilirubin-excretory power of the liver cell may be utilized as an excellent test of liver function. Prolonged retention of injected bilirubin may be the only demonstrable evidence of a cellular dysfunction

REFERENCES

- ¹ROSENTHAL, F. Die Bedeutung des Elastins beim Icterus, *Klin Wchnschr*, 1930, ix, 1909-1913
- ²VIRCHOW, R. Die pathologischen Pigmente, *Arch f path Anat u Physiol u f klin Med*, 1847, i, 379-491
- ³MINKOWSKI, O. and NAUNYN, B. Beiträge zur Pathologie der Leber und des Icterus, *Arch f exper Path u Pharmacol*, 1886, xxi, 1-33
- ⁴LOWITZ, M. Beiträge zur Lehre vom Icterus, *Beitr z path Anat u z allg Path*, 1889, iv, 225-264
- ⁵MCNER, J. W. Experiments on hemolytic

- icterus, Jr Path and Bact, 1913-14, xviii, 325-342
- ⁶WHIPPLE, G H, and HOOPER, C W Icterus, a rapid change of hemoglobin to bile pigment in circulation outside the liver, Jr Exper Med, 1913, xvii, 612-635
- ⁷RICH, A R Formation of bile pigments, Physiol Rev, 1925, v, 182-224
- ⁸MAKINO, J Beitrage zur Frage der anhepatocellularen Gallenfarbstoffbildung, Beitr z path Anat, u z allg Path, 1924, lxxii, 808-859
- ⁹MANN, F C Relation of the liver to metabolism, Harvey Lect, 1927-28, Ser xxiii, Williams and Wilkins Company, Baltimore, 49-75
- ¹⁰ROSENTHAL, F, MELCHIOR, E, and LICHT, H Untersuchungen am leberlosen Säugetier, Arch f exper Path u Pharmakol, 1925, cvii, 238-259
- ¹¹JOANNOVICS, G, and PICK, E Beitrag zur Kenntnis der Toluyldiaminvergiftung, Ztschr, f exper Path u Therap, 1910, vii, 185-214
- ¹²KODAMA, M Beitrage zur Pathogenese des Ikterus, Beitr z path Anat u z allg Path, 1925, lxxiii, 187-250
- ¹³HALDEMAN, K O A histologic study of formation of bile pigment, Arch Path, 1929, vii, 993-1011
- ¹⁴ERNST, Z, and SZAPPANIOS, B Untersuchungen über extrahepatogene Gallenfarbstoffbildung an überlebenden Organen, Biochem Ztschr, 1925, clvii, 16-29
- ¹⁵KOMORI, Y, IWAO, C, and NAKAMURA H Über die Bilirubinbildung der Überlebenden normalen Milz, Jr Biochem, 1928, viii, 195-204
- ¹⁶LEPEHNE, G Pathogenese des Ikterus, Ergebn d inn Med u Kinderh 1921, xv, 221-280
- ¹⁷EPPINGER, H Ikterus, Neue deutsch Klin, 1930, v, 274-303
- ¹⁸ROLLESTON, H, and MCNEE, J W Diseases of liver, gall bladder and bile ducts, 1929, Macmillan Company, New York, 568
- ¹⁹STUBER, B Klinische Physiologie, 1927, J F Bergmann, München, 263
- ²⁰RICH, A R (Quoted by Barron No 22)
- ²¹RICH, A R Pathogenesis of forms of jaundice, Bull Johns Hopkins Hosp 1930, xlii, 338-377
- ²²BARRON, E S G Bilirubinemia, Med, 1931, v, 77-133
- ²³MCMASTER, P D, and ELMAN, R Urobilin physiology and pathology, Ann Int Med, 1927, i, 68-73
- ²⁴BERGMANN, G Zur Funktionellen Pathologie der Leber insbesondere der Alkohol-Aetiologie der Cirrhose, Klin Wchnschr, 1927, vi, 776-780
- ²⁵EILBOTT, W Funktionsprüfung der Leber mittels Bilirubinbelastung, Ztschr, f klin Med, 1927, cvi, 529-558
- ²⁶HARROP, G A JR, and BARRO, E S G The excretion of intravenously injected bilirubin as a test of liver function, Jr Clin Invest, 1931, x, 577-587

Niemann-Pick's Disease^{*,†}

(Essential Lipoid Histiocytosis)

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NIEMANN-PICK'S disease is a disease of infancy characterized clinically by an enlargement of the liver, spleen and lymph glands, associated with yellowish brown pigmentation of the skin and accompanied by an enlarged abdomen and more or less emaciation. Cranial and skeletal changes may be associated. It is a fatal condition, being characterized by progressive wasting. Death may be due to intercurrent affections. "It is a congenital, familial, constitutional, systemic disease which manifests itself as a disturbance of the lipoid metabolism and leads to a deposit of complex cellular substances in the cells of the reticulo-endothelial apparatus. Its etiology and pathogenesis are unknown. It does not yield itself to therapy."¹

In 1914, Niemann² described a peculiar form of splenohepatomegaly, occurring in an infant, which was fatal at eighteen months. Since that time, several cases have been reported. Extensive clinical and pathological studies have been made. These include cases reported by Knox, Wahl and Schmeisser,³ Siegmund-Koln,⁴ Bloom,⁵ Hen-

schon,⁶ Schiff,⁷ Hamburger,⁸ Corcan, Oberling and Dienst,⁹ Berman,¹⁰ Kramer,¹¹ Dienst and Hamperl,¹² Abt and Bloom,¹³ and Abrikossoff¹⁴.

Berman, in his report of a case in a girl of fifteen months, records the history of vomiting and abdominal distention since the second month of life. Enlargement of the liver and spleen was recognized at six months. Splenic puncture showed typical foamy cells and, at autopsy, the splenic pulp was found to be made up almost entirely of foamy cells, large, round, vacuolated and pale. He also reported a fractional determination of the blood lipoids.

Kramer's case was of a girl of fourteen months. The spleen had been enlarged since she was four months of age. Examination of the spleen, after a splenectomy, showed the tissues almost completely replaced by masses of large, pale cells of varying shapes with small nuclei.

Abrikossoff's case showed a moderate enlargement of the spleen and extensive involvement of the cranial and general skeletal structures. This, perhaps, justifies the assumption of a skeletal type of Niemann-Pick's disease after the manner of a skeletal type of Gaucher's disease.

Bloom and Kern¹⁵ concluded, from chemical analysis of the spleen, that, in

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Niemann-Pick's disease, the stored material is chiefly phosphatids, probably lecithin and cholesterol. While in Gaucher's disease, the stored material is kersin.

In both cases, these pathological substances are deposited in the liver and spleen causing a marked enlargement of these organs.

The composite clinical picture presented by Abt and Bloom¹³ might, in many respects, be that of our case. The patient was mentally and physically retarded. The facies strongly suggested mongolianism. He could not stand, when he assumed a sitting posture, the head and shoulders drooped forward exhibiting a decided curve of weakness. There was little

interest manifested in what went on about him. Toys held no allurements. For the most part, he was content to lie quietly taking only a brief interest in the attendant, other children at play and even in his food. The temperature fluctuated, and his leukocytosis reached 22,400. The accompanying photographs portray the mongoloid appearance and the large ascitic abdomen. (Figures 1 and 2) After tapping, the decidedly enlarged liver and spleen were found to extend as low as the crests. (Figure 3)

Palpation and x-ray of the spine demonstrated an abnormality, probably a congenital defect. X-ray of the chest revealed alterations of the ribs, probably the bony involvement to which



Fig 1 Mongoloid appearance, ascites and edema of scrota in Niemann-Pick's disease



Fig 2 Marked ascites associated with hepatosplenomegaly. Niemann-Pick's disease

Abrikossoff¹¹ called attention. An abnormal condition of the maxilla might be congenital or, more probably, further evidence of bony change indicating cranial involvement

CASE REPORT

Frank S, white, Austrian, twenty months old, was admitted to the Children's Department of the Washington Hospital, August 24, 1929, because of an enlarged abdomen

Five weeks prior to admission, he had an acute febrile disorder accompanied by an eruption which was probably measles. Two weeks before admission, the mother noticed his abdomen "seemed swollen" and had become progressively larger. At about the same time, she noticed that he was slightly jaundiced

Past History He was born December 13, 1927. Labor was easy, delivery spontaneous.

There were no birth injuries, cyanosis, hemorrhage or convulsions. He was the fourth child, full term breast fed until admitted to the hospital. He had had no previous illness except measles. He sat up at eight months, first tooth erupted at ten months. His first words were spoken at one year. At fifteen months, he was able to stand, using his crib as support. He was able to take a few steps at the age of seventeen months.

Family History. Father, mother and two sisters living and well. One brother died three days after birth, cause unknown. Neither of the two sisters shows any abnormality nor is there any history of illness comparable to the patient's disease in either the paternal or maternal families.

Physical Examination He was a rather poorly nourished and developed child of about twenty months, whose mental development seemed below that of the average in-

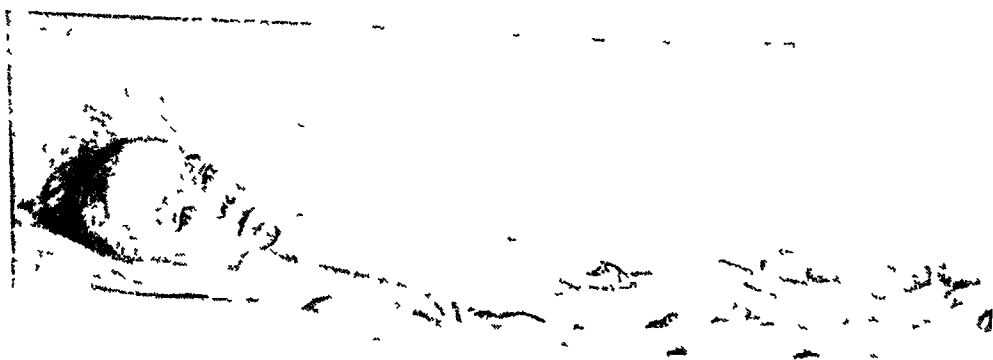


Fig 3 The same patient after withdrawal of the ascitic fluid

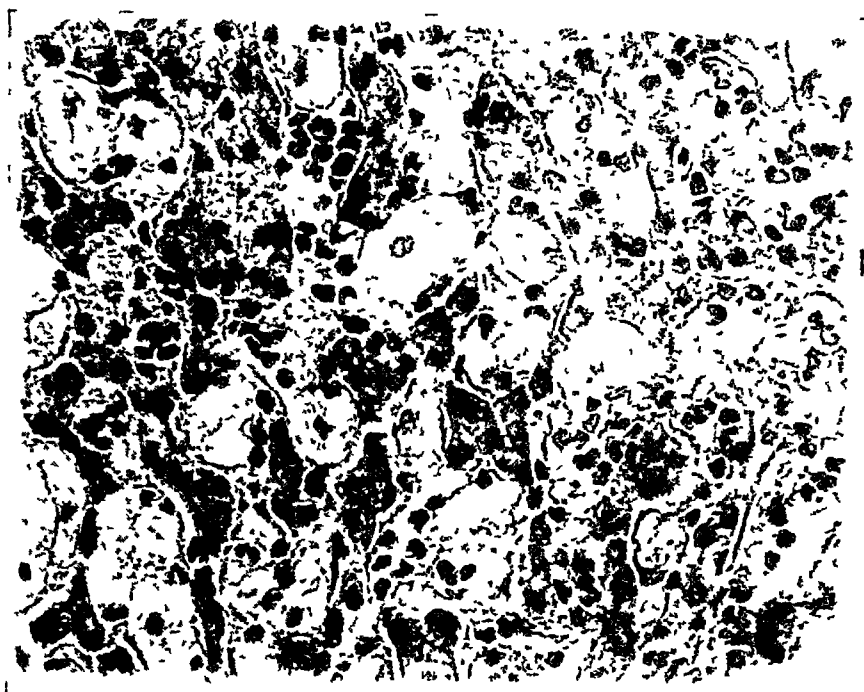


FIG 4 Cholesterolosis of reticulo-endothelial cells of liver sinusoids

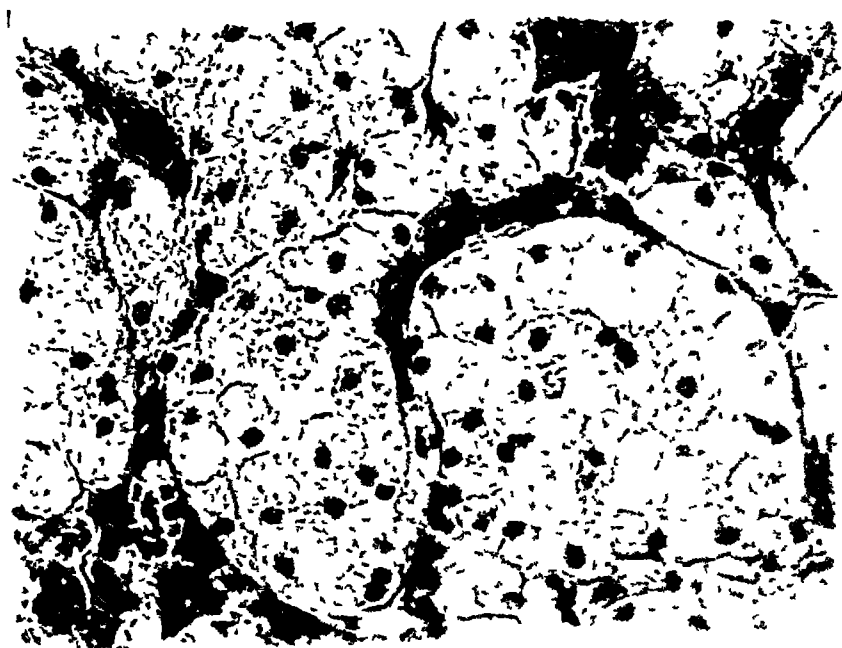


Fig 5 More marked separation of liver cells by masses of foamy cells in the intercordal sinusoids

fant of this age. There was a slight yellowish pigmentation of the skin. The head was of the square type and seemed somewhat large in proportion to the rest of his body, circumference 50 cm. The anterior fontanel was almost closed. The sclera was distinctly visible above the cornea, the pupils were equal and reacted to light. Ears were negative. There was a marked mucopurulent discharge from each nostril, teeth were poorly developed and irregularly spaced, the alveolar process, on the left, was widened and partially covered with a white exudate. Tongue was thickly coated with a grayish brown exudate. There was mild inflammation of the mucous membrane of the pharynx. The anterior and posterior cervical glands were palpable. There was a questionable rigidity of the neck, the thorax seemed flattened antero-posteriorly and the costal margins flared outward and upward. The lungs were resonant, breathing was not labored but respirations were accompanied by distress. The apex beat of the heart was in the fourth intercostal space in the mid-clavicular line, impulse was barely felt, the sounds were clear and regular. The abdomen was markedly distended, showing many dilated veins. The abdominal wall was tense, there were signs of fluctuation, no masses could be felt. Genitalia were normal except for first degree hypospadias. The vertebral column showed a prominence in the lower lumbar region. It was widened and irregular. Bony prominences were felt laterally to the spinal processes which seemed to be more widely separated than normal. The extremities were swollen. The surface temperature of the hands and arms was below normal but less than that of the feet and legs which was distinctly cold. There was some swelling but no pitting on pressure. The reflexes were diminished or absent. By high rectal examination, a mass could just be felt.

The day following admission, respirations were more embarrassed and the abdomen was tapped and 3200 cc of straw colored fluid was removed, following which he was relieved. The abdomen was quite flaccid. The liver and spleen were both enlarged. The liver could be felt as low as the umbilicus in the midline and extended downward almost

to the crest of the right ilium. The spleen extended downward almost to a corresponding point on the left. Both masses were firm, hard and smooth with the exception of a nodule which seemed to be attached to the outer surface of the spleen.

Two weeks later, the abdomen seemed to be refilling. The head appeared larger, the circumference was 50.5 cm. The child took very little interest in his surroundings and was not eating well.

On September 18, the abdomen seemed to be increasing in size. The circumference of the head was 50.1 cm. Its maximum of 51.2 cm was reached one month after admission.

The spinal fluid was clear, globulin was increased, no increase in cells. Kahn test on the spinal fluid was negative. His blood picture, on admission, was Hemoglobin, 75 per cent, red blood cells, 4,530,000; white blood cells, 7,100, polymorphonuclears, 68 per cent, lymphocytes, 24 per cent; endothelial leukocytes, 4 per cent.

There was a progressive change from this picture to that of February, 1930, which was Hemoglobin, 65 per cent, red blood cells, 3,420,000, white blood cells, 22,400.

The urine showed at intervals a trace of albumen and, at times, rather numerous hyaline casts with some few white blood cells.

Aside from a mild bronchopneumonia in November, 1929, there was nothing unusual in his progress. He lost weight intermittently and failed rather steadily throughout the course of the disease which was terminated by death, February 22, 1930, almost six months after his admission.

Pathological Report The body is that of an emaciated child approximately two years old. The feet, legs, scrotum and penis are edematous. Congenital defects present are hypospadias and occult spina bifida in the lumbar region. There is marked distention of the abdomen and eversion of the costal margin. The head is large and square. The anterior fontanel is not completely closed. There is a deficient growth of hair on the head. The face has an aged appearance. Palpation gives one the impression of a mass below the right costal margin. There appear also to be masses in the lower abdomen.

The lungs are pale and grossly do not show

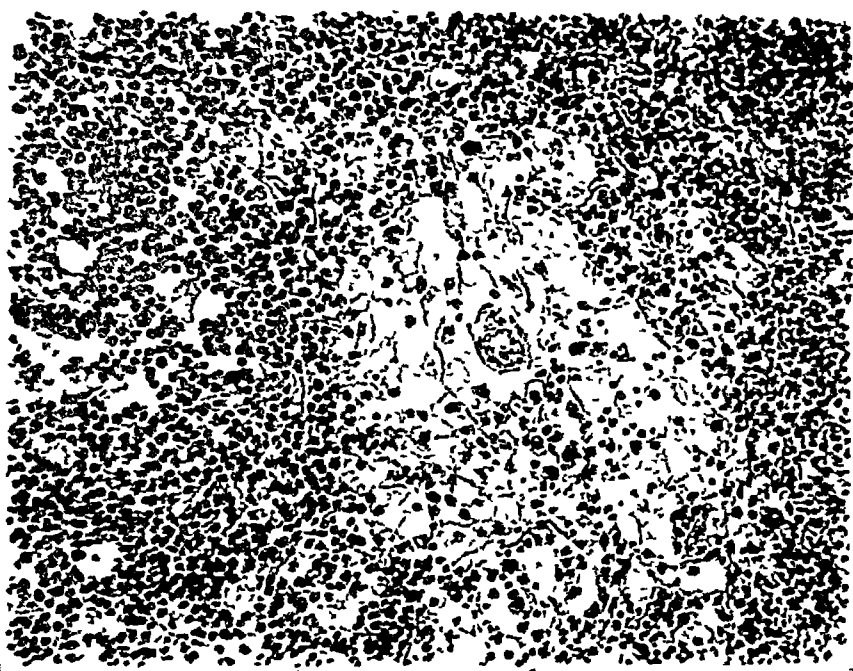


FIG 6 Groups of foam cells, lipid-containing reticulo-endothelial cells, in the spleen

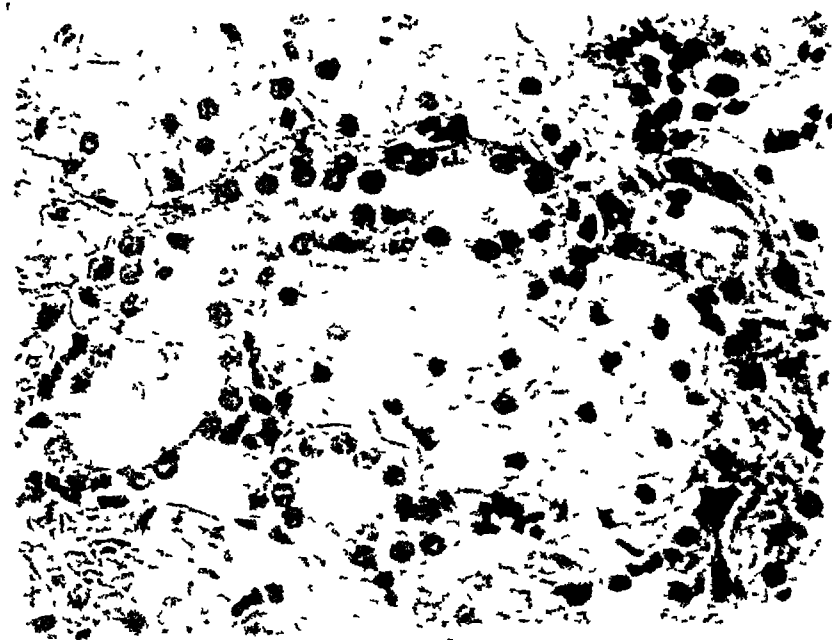


Fig 7 Intertubular masses of iron-containing cells

suggestive changes. The lymphatic glands at the hilus are enlarged.

The heart has a pallid appearance but otherwise shows no pathological lesions.

The intestines are matted together and adherent to the parietal wall. The adhesions are dense and difficult to break up. Between the coils are found pockets of clear, yellowish colored fluid which is partly coagulated. The mesenteric and retroperitoneal lymph nodes are enlarged.

The liver is covered with a thick, grayish white membrane and is adherent both to the intestine and diaphragm. Separation of these adhesions is difficult. The organ is enlarged, especially the right lobe. On the under surface of the right lobe, there is a longitudinal fissure in which there is a grayish white nodule one centimeter in diameter. On section, the liver cuts with increased resistance and the cut surface bulges. The cut surface is of a pale, grayish color, with a mottling of irregular lighter areas.

The spleen is only moderately increased in size and shows a marked hyalo-capsulitis. On section, it cuts with increased resistance, the cut surface bulges and is of a dark red color with small irregular patches of a paler hue. The splenic corpuscles are indistinct.

The kidneys are of approximately normal size, pale, and the capsules strip readily. The cut surface is pale with a mottling of lighter areas. The medullary rays and pyramids are indistinct.

The spinal canal was opened at the point of the spina bifida and was found to contain a large quantity of clear yellowish fluid, partly coagulated. Gross lesions were not found in the cord.

The cortex of the ribs is thin and friable. The cancellous tissue is rarefied and paler than normal.

Microscopical Examination Sections from all the organs examined show extensive involvement with large, flat, irregular, round or polyhedral cells having small nuclei which are usually eccentrically located. The cell cytoplasm is finely granular, vacuolated and shows a delicate reticular structure. These cells apparently have their origin from the reticulum lining cells of the various organs.

Sections from the lungs show irregular groups of alveoli distended with these cells and compressing adjacent capillaries. The larger vessels are surrounded by wide mantles of the cells which have replaced the adventitia and the greater part of the media while the intima remains intact.

Sections from the liver show a diffuse involvement. In the periportal tissue the bile ducts and blood vessels are surrounded by these cells. In the parenchyma, the sinusoids are distended, the adjacent cells compressed and atrophic (figures 4 and 5). Wide areas show complete absence of liver cells, the new cells lying in a reticulum consisting of remnants of the walls of the sinusoids. In the nodular area, the cells are growing either diffusely or in small and large alveolar formation. Here also, the cells lie in a reticulum arising from the walls of the sinusoids.

Sections from the spleen (figure 6) show involvement of the capsule, pulp and splenic corpuscles. The cells are found about and within the corpuscles and in many cases only a trace of the lymphoid tissue remains. The splenic venules are involved in small and large irregular areas. The venules surrounding the involved parts are engorged with blood.

In the kidneys (figure 7) the cells are found growing either diffusely or in small and large alveolar arrangement surrounded by a delicate limiting membrane which is apparently derived from the kidney reticulum. In the involved areas these cells have largely replaced the kidney tubules. The glomerular tufts are also involved, practically all showing partial destruction of their normal structure and replacement with these new cells.

In the spinal cord, the cells are packed around the nerve elements which are degenerated and atrophic, many having disappeared completely.

The reticulum of the sympathetic ganglia also shows large groups of the characteristic foam cells (figure 8).

Sections from the ribs show the cortex thinned and immediately beneath it broad sheets of large pale cells surrounding a few fragments of bone trabeculae. Centrally, very little bone structure remains (figure 9).

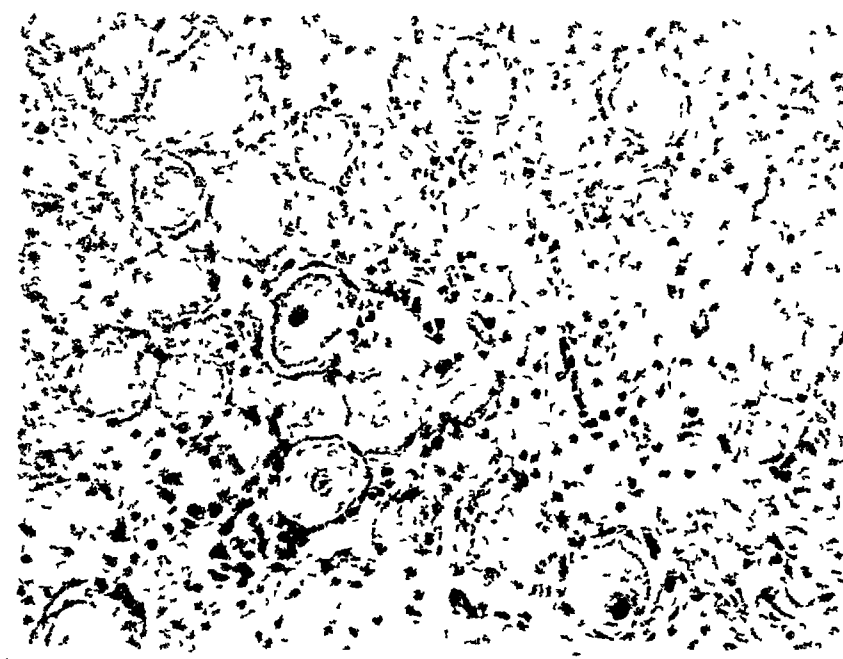


FIG 8 Sympathetic ganglion with foam cells in the reticulum

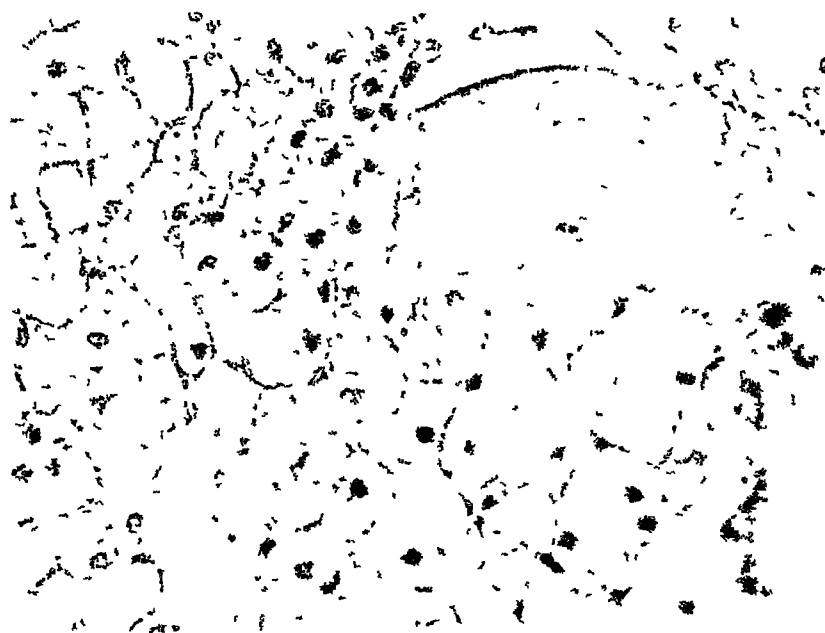


FIG 9 Osteoporotic bone with marrow entirely replaced by cellular mass

The blood forming islands are invaded and greatly reduced in number. There is no evidence of osteoclastic activity by these cells but rather bone destruction seems to result from pressure atrophy.

Sections from a lymph node show the normal architecture destroyed. The new cells lie in a reticulum derived from the original structure. Only traces of lymphoid cells remain.

After mordanting the sections with bi-chromate of potassium, the fat in the cells takes a dark yellow stain with scarlet red and appears both as minute and medium sized globules.

A consideration of the extensive involvement of the various organs, the

evident relationship of the cells to the reticulo-endothelial system, the presence of fat in the cells and the absence of non reaction as in Gaucher's disease, together with the age and early fatal outcome would seem sufficient evidence to establish this as a case of Niemann-Pick's disease.

Acknowledgment of our appreciation is hereby made to Dr F. I. Patterson, who contributed to the care of this child.

Photomicrographs accompanying this article were made possible through the courtesy of Dr E. T. Bell and his staff of the University of Minnesota.

REFERENCES

- ¹STEINER, W. R. Diseases of the spleen, Nelson's Loose Leaf Med, 1929, 609-614.
- ²NIEMANN, A. Ein unbekanntes Krankheitsbild, Jahrb f Kinderh 1914, xxix, 1-10.
- ³KNOX, J. H. M., Jr, WAHL, H. R., and SCHMEISSER, H. C. Gaucher's disease a report of two cases in infants, Johns Hopkins Hosp Bull, 1916, xxvii, 1-12.
- ⁴SIEGMUND-KOLN. Lipoidzellenhyperplasie der Milz und Splenomegalie Gaucher, Verhandl d deutsch path Gesellsch, 1921, xviii, 59-62.
- ⁵BLOOM, W. Splenomegaly (type Gaucher) and lipoid-histiocytosis (type Niemann), Am Jr Path, 1925, 1, 595-626.
- ⁶HENSCHEN, F. Contribution à l'étude de la maladie de Gaucher, Acta Med Scandinav, 1925, xvi, 593.
- ⁷SCHIFF, E. Im Leben diagnostizierte lipoidzellige Splenohepatomegalie (Typus Niemann-Pick) bei einem 17 Monate alten Knaben, Jahrb f Kinderh, 1926, lxii, 1-6.
- ⁸HAMBURGER, R. Lipoidzellige Splenohepatomegalie (Typus Niemann-Pick) in Verbindung mit amaurotischer Idiotie bei einem 14 Monate alten Mädchen, Jahrb f Kinderh, 1927, cxvi, 41-50.
- ⁹CORCAN, P., OMBLING, C., and DIENST, G. La maladie de Niemann-Pick, Rev. franç de pédiat, 1927, iii, 789-829.
- ¹⁰BIRMAN, S. L. A case of lipoid histiocytosis, Am Jr Dis Child, 1928, xxxv, 102-114.
- ¹¹KRAMER, B. Lipoid-cell splenohepatomegaly, Niemann-Pick type, a clinical analysis of nine cases with a report of one additional case, Med Clin N Am, 1928, xi, 905-918.
- ¹²DIRNST, and HAMPEL, H. Berichten über einen Fall von lipoidzelliger Splenohepatomegalie vom Typus Niemann-Pick, Wien klin Wchnschr, 1927, xi, 1432-1433.
- ¹³ABT, A. F., and BLOOM, W. Essential lipoid histiocytosis (type Niemann-Pick), congenital disturbance in lipid metabolism in infants associated with splenohepatomegaly, Jr Am Med Assoc, 1928, xi, 2076-2080.
- ¹⁴ABRIKOSOFF, A. Demonstration eines eigenartigen Falles der Niemann-Pick'schen Krankheit, Centralbl f allg Path u path Anat, 1928, xliii, 7.
- ¹⁵BLOOM, W., and KERN, R. Spleen from Gaucher's disease and lipoid histiocytosis, Arch Int Med, 1927, xxix, 456.

Four Physiologic Defenses of the Upper Part of the Respiratory Tract: Ciliary Action, Exchange of Mucin, Regeneration and Adaptability*†

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I SHALL give the results of some studies in connection with a tremendously interesting and but poorly understood structure, namely, the mucosa of the upper part of the respiratory tract. This work resulted from a study of the common cold.³ In connection with that, the textbooks and periodicals were thoroughly searched for an adequate discussion of the physiology and pathology of the nasal mucosa. Nothing satisfactory was found anywhere. Consequently, I began a special physiologic study.

In this presentation, four factors in the armamentarium of defense of the nasal mucosa will be considered. They are ciliary activity, exchange of mucin, regeneration, and what might be termed adaptability to environment. The regeneration meant is that repair which follows injury to the surface, as in the common cold.

The purpose of the presentation is to emphasize the great activity of this extremely delicate and much exposed

membrane. I think there is no structure in the body so delicate and so severely exposed to the environment as the nasal mucosa. One would expect an inert, resistant, leathery type of epithelium in such an exposed position. Instead there is a highly specialized, ciliated, fragile membrane. It exists, I believe, largely by virtue of its remarkably active systems of defense.

CILIARY ACTIVITY

Ciliary activity in general is well understood. Biologists and physiologists have developed the knowledge of this phenomenon in great detail. This knowledge, however, has not been applied to the nasal mucosa in an adequate fashion. Its importance has not been sufficiently stressed.

The motion of the cilia of the nasal mucosa of man is simple, whip-like and in two phases, there is an active phase in the direction of the flow of over-lying material and a phase of recovery. The rate is approximately 250 cycles a minute. The action is coordinated in a very remarkable manner. When viewed in profile the cilia are seen to beat in sequence in such a way that waves are formed and travel across the surface. When viewed from above, as seen in a field of granules, the cilia pass over the granules in a regular pattern. No two cilia are in phase.

*Read before the American College of Physicians, San Francisco, California, April 5, 1932, with motion picture demonstration.

†From the Section on Ophthalmology, The Mayo Clinic, Rochester, Minnesota. Work done in the Division of Experimental Surgery and Pathology, The Mayo Foundation.

wave are in exactly the same phase at any moment. When viewed from the front, on the other hand, rather small groups beat in unison. In military language, the ranks beat in unison and the files in sequence. In larger fields observed from above, I have received the impression at times that they are divided into strips that coordinate in such a way that adjacent strips beat more or less alternately. This would provide a hand-over-hand action that would greatly increase the effectiveness of the cilia in moving along the covering film of mucin. It is difficult to make certain that this hand-over-hand action is normal because it can be seen distinctly only when the ciliary beat is abnormally slow. The power of ciliary action is much greater than is ordinarily supposed. These tiny, hair-like processes, only five or six microns in length, move comparatively huge loads of overlying material that may be more than a hundred times as thick as the length of the cilia. The efficiency of ciliary action increases under loads until an optimal pressure has been exerted, and then decreases. The optimal pressure in the case of the epithelium from the pharynx of the frog is said to be about twelve grams per square centimeter.⁷ It is said to be less in the nose of man. In any case, the weight of the secretion in a mucin-filled maxillary sinus would not be sufficient to depress ciliary action on the floor, but would serve rather to stimulate it.

The question of ciliary control has not been settled. The action itself is automatic. Detached cells continue active, and even single detached cilia will beat if a bit of cytoplasm remains attached to them, as can be seen in mo-

tion pictures that I have made. In addition to the automatic action there must be a control of some type in order to produce that remarkable coordination. Whether it be nervous⁸ or on some other basis,⁹ is of no particular concern in this presentation.

EXCHANGE OF MUCIN

The speed of ciliary motion is bound up with the nature and the depth of the overlying film. Normally, the moist film that covers the nasal surfaces is a very thin, rather highly viscid, mucinous secretion. In a sense it is like one large, intact membrane or web that overlies all surfaces within the nose, sinuses, pharynx and esophagus. This web moves throughout its extent continuously. It has a certain tensile strength, and can sustain traction. This is a very important feature. There are some regions within the nose that normally are nonciliated. The web of mucin moves across these by means of traction exerted on it by the ciliated regions. From my studies it appears to me that this traction on the mucin is one of the most important factors in the successful accomplishment of normal drainage of the nose and sinuses. Gravity, on the other hand, plays only an incidental part, and is often a handicap rather than an aid.

The web of mucin moves backward within the nose over a fairly definite system of drainage, at widely varying rates of speed.⁶ Both rate of speed and direction are determined largely by the relation of the ciliated to the nonciliated areas. The regions in which the inspired air first makes impact are nonciliated.⁶ These vary somewhat in position and extent, according to indi-

vidual anatomic variations, but in general include the preturbinal region on the lateral wall, the anterior ends of the middle and inferior turbinates, and the anterior fourth of the septum. The presenting surfaces of spurs and ridges may likewise be nonciliated. The remaining surfaces, including the posterior two-thirds or three-fourths of the nose (exclusive of the olfactory region) are ciliated. In these studies the system of drainage was mapped by dotting drops of India ink over the surfaces and observing the direction and rate of flow as they moved back to the nasopharynx. The rate of flow over the ciliated areas was found to be comparatively great; namely, four to six millimeters a minute, whereas over the nonciliated areas, it was only a few millimeters an hour.

The direction of flow in the ciliated regions in general was backward, with a slight downward tendency. Over the

middle and inferior turbinates there was found a strong tendency for the flow to be diagonally downward, across the inferior border, into the corresponding meatus (figure 1). Apparently the reason for this is that the cilia are more active in the protected middle and inferior meatuses than in the more exposed, common meatus. In those regions, then, the web of mucin moves faster, and through traction drags the mucin from the areas of slower motion on the mesial side of the turbinates into the meatuses. It follows that the mucin does not necessarily flow exactly in the line of the direction of the beat of the cilia immediately underlying. Through traction it may slide diagonally across that line.

The direction of flow in the nonciliated regions appeared to be determined almost entirely by traction from the middle and inferior meatuses (figure

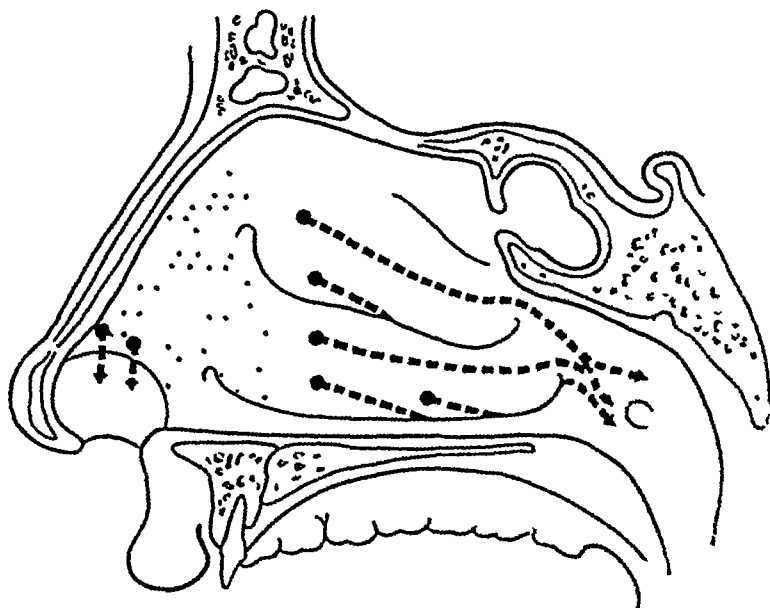


FIG. 1. The direction of the normal flow of mucin over the ciliated surfaces of the lateral wall of the nose. The flow along the indicated lines is rapid. The dotted areas are nonciliated.

2) The motion was very slow. The lines followed by the ink converged at the anterior attachments of the turbinates and disappeared into the meatuses to emerge at the posterior ends. In a word, the nonciliated, inactive areas on the lateral wall drain very largely through the inferior and middle meatuses. It is to be remembered that this is the region in which dust, bacteria, cosmetics, and other foreign materials are most likely to lodge. Therefore, this foreign material drains back through the meatuses.

The drainage on the septum was found to be similar to that of the lateral wall. There was an inactive, nonciliated area anteriorly that drained very slowly through traction exerted on the web of overlying mucin. The rate was only a few millimeters an hour. Behind this area the surface was found to be very active (except on ridges and spurs) and ink drained at the rate of three to six millimeters a

minute. It took from only three to ten minutes for the ink to traverse the distance from the anterior third of the septum to the posterior margin.

In general, then, it may be said that the mucinous film covering the surfaces of the posterior two-thirds of the nose is replaced every ten or fifteen minutes. The film over the anterior third is renewed only about once each hour or two, and drains away through the meatuses. This may explain the fact that cultures made from deep in the nose are so often sterile.¹ Very few bacteria lodge deep in the nose, and those that do lodge there are swept away quickly. The regions where they lodge in large numbers drain very largely through the meatuses, where cultures are not usually taken.⁴

RAPID REGNERATION

Microscopic studies of warm, fresh secretion derived from patients with early colds, and of specimens removed

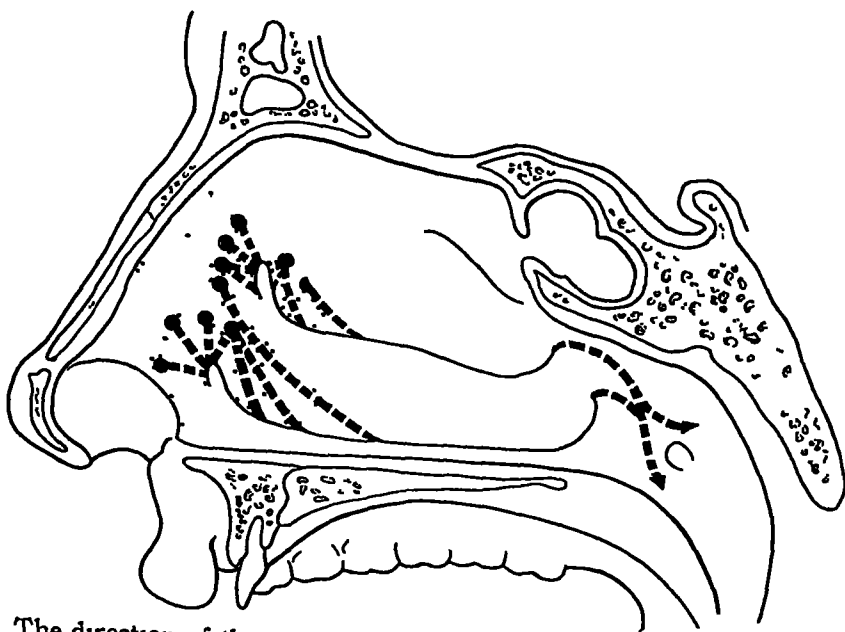


FIG 2 The direction of the normal flow of mucin as it is drawn by the cilia of adjacent areas over the nonciliated mucous membrane in the anterior portion of the nose. The lines converge at the anterior attachments of both turbinates, indicating that the mucin is drawn into the meatus.

for biopsy in the course of colds indicate clearly that there is extensive loss of the cells from the lining mucous membrane in the course of the common cold. In the first three days there are often great numbers of living ciliated and nonciliated epithelial cells floating free in the secretion (figure 3). During these days such cells greatly exceed the leukocytes in number. The nonciliated forms are the immature replacement cells normally found deep in the epithelium. Their presence indicates that the destruction goes deeply into the epithelium. This has been found to be the case in specimens removed for biopsy. Sometimes there is only a single layer of cells left in place

on the basement membrane.³ Yet it is rare that true ulceration occurs or that the underlying tissues are destroyed. It is inferred that the epithelial cells slough out in response to surface irritation and are replaced repeatedly with facility and great rapidity. The injury goes deep into the epithelium and causes extensive destruction, yet in a few days the epithelium is once more entirely normal.

ADAPTABILITY

The finding of active and inactive areas of drainage within the nose, and the determination that the mucous membrane of the active areas was ciliated and that of the latter nonciliated,



FIG. 3. Epithelial cells and leukocytes found in the secretion in the course of a cold. Most of the cells are epithelial cells.

suggested study of histologic changes in the epithelium after the normal ventilation had been altered experimentally. The point to be determined was whether the various types of epithelium within the nose and sinuses are produced by variations in exposure to flow of air in the individual case, or whether the inference is that they are produced only by long ages of evolution. Two series of experiments were performed. The results indicated clearly that the nasal mucosa has a chameleon-like property of altering its form radically, according to circumstances.

In one series of experiments the right nostril of each of eight rabbits and of two dogs was closed surgically, causing the animals to breathe through one side of the nose only. The animals were killed after periods varying from

three weeks to six months, and sections from various parts of the nose were examined microscopically. There were marked changes on both the open and the closed sides in the rabbits. In the dogs there were marked changes on the open side only.

The histologic alterations on the septum on the side of the open nostril were in the nature of an extension backward of the area of squamous-like epithelium normally found just posterior to the vestibule. In those animals that lived longer, this type of epithelium extended well over half the length of the septum. The cilia were lost and the cells became stratified (figure 3). Going further backward, it was found that the epithelium became transitional and finally columnar. The mucous membrane of the elaborate turbinate became stratified and very much thick-

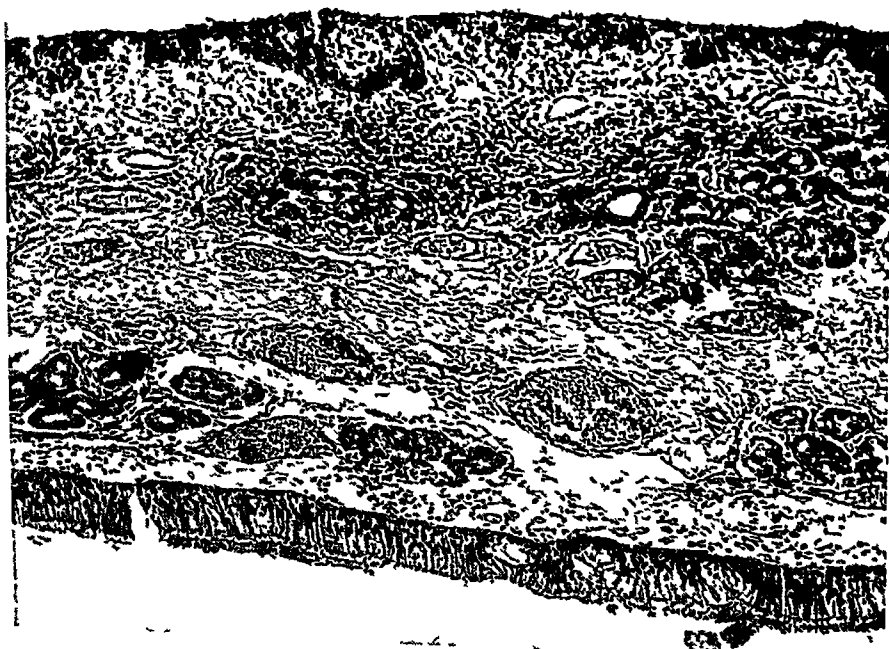


FIG 4 Section through the nasal septum of a dog four months after surgical closure of one nostril. The epithelium of the open side is uppermost. There is a marked change from the high columnar of the closed side to the squamous-like epithelium of the open side.

er than normal. In the meatuses the cuboidal epithelium became columnar, and short columnar epithelium became tall columnar. Within the sinuses there was practically no change. In a word the degree of change was proportional to the exposure to the impact of inspired air.

In the rabbits there was a very marked change on the closed side also. The distribution was similar to that of the changes on the open side, greatest on the anterior part of the septum, and least within the sinuses. It consisted in a very great increase in the numbers of goblet cells, that is, non-ciliated, mucin-filled cells. Over the anterior portion of the septum every cell, practically, became a goblet cell some months after closure of the nostril. Further back on the septum, ciliated cells also appeared. About half way back there were equal numbers of ciliated and goblet forms, and the further back the examination was carried the greater the number of ciliated cells and the fewer the number of goblet cells found. There was also a marked increase in number of goblet cells over the turbinates, the number became progressively less marked posteriorly. This increase in goblet cells was not noted within the sinuses.

In another series of experiments the frontal sinuses of a number of dogs were fully exposed to the outer air by removal of the roof and overlying skin. This sinus epithelium also changed markedly. It changed from cuboidal to columnar in the spots that were best protected and became stratified in the most exposed spots.

These experiments indicate several things. First, it seems certain that the

epithelium can alter its form radically in a comparatively short time, according to the demands made on it, and the various pictures of epithelium found do not represent different types of epithelium, but merely various forms of the same general respiratory epithelium. These experiments point to a probable explanation of the islands of squamous epithelium so commonly found in the trachea. Doubtless there are eddies in the streams of respired air that strike the tracheal wall with some force in those areas. The fact that there was no change in the sinus epithelium, either on the closed or on the open side in the series of cases in which one nostril had been closed, indicates that ventilation of the ostia of the sinuses may not be as essential as has been believed. The accidental finding of the tremendous increase in mucin-containing cells suggests the possibility that goblet cells represent only a phase in the life cycle of the ciliated columnar cell. Perhaps instead of two types of cells in this epithelium there is only one type.

SUMMARY

The epithelium of the upper part of the respiratory tract is not simply a static structure, with a feeble tendency to move overlying materials. It is dynamic. It is intensely active. The ciliary beat with extreme rapidity and moves tremendous loads of mucin and foreign material with speed, power, and efficiency. The ciliary motion is dependent on the overlying film of mucin that is so much like another living membrane. In the major portion of the nose this film of mucin is continuous.

frequently. It may be said that there is a complete new lining over all the ciliated areas every ten or fifteen minutes. These portions are generally sterile. Even the nonciliated, inactive areas in the anterior fourth of the nose have an exchange of mucin every hour or two. When an irritant attacks from the surface, the mucosa sloughs its injured cells readily, before they are dead, and replaces them very quickly.

Prolific regeneration seems to be part of the physiologic process. Under certain conditions the percentage of goblet cells contained can be made to increase very greatly. When very much exposed to the force of flowing air and foreign particles, the epithelium of the membrane is altered in form from ciliated columnar to squamous-like. It ceases its tremendous activity, and becomes passively resistant and inert.

REFERENCES

- ¹ARNOLD, LLOYD, OSTROM, M. L., and SINGER, CHARLOTTE. Autosterilizing power of the nasal mucous membrane, *Proc Soc Exper Biol and Med*, 1928, *xxv*, 624-627.
- ²GRAY, J. Ciliary movement, New York, Macmillan Co., 1928, 170 pp.
- ³HILDING, ANDERSON. The common cold, *Arch Otolaryngol*, 1930, *xii*, 133-150.
- ⁴HILDING, ANDERSON. The influence of ciliary activity on the bacteriology of the nose, *Proc Staff Meetings of Mayo Clinic*, 1931, *vi*, 320-321.
- ⁵HILDING, ANDERSON. The physiology of drainage of nasal mucus, *Arch Otolaryngol*, 1932, *xv*, 92-100.
- ⁶HILDING, ANDERSON. Experimental surgery of the nose and sinuses. 1. Changes in morphology of the epithelium following variations in ventilation, *Arch Otolaryngol*, (in press).
- ⁷MAXWELL. Quoted by Gray.
- ⁸MCDONALD, J. F., LEISURE, C. E., and LINNIMAN, E. E. New principles in the control of the activity of ciliated epithelium. *Tr Am Acad Ophth and Oto-Laryngol*, 1928, 318-354.
- ⁹PARKER, G. H. The elementary nervous system, London, J. B. Lippincott Co., 1919, 229 pp.

Paranasal Sinusitis

A Problem in General Medical Practice*†

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THE etiologic relationships of paranasal sinusitis** to systemic disease belong to the unsolved problems of clinical medicine. This is shown by the relatively increasing frequency with which patients suffering from conditions which may be referable to sinus disease find their way into the hands of consultants. The possibility of sinusitis as a causative factor must occur not infrequently to every physician who sees in chronic localized infection the solution of a considerable number of obscure diagnostic and therapeutic problems. Occasionally gratifying results have followed treatment advised on the basis of sinus etiology. However, failures have been so disappointingly frequent

that skepticism and prejudice have tended to so displace rational thinking in the minds of many physicians, that some have come, as a matter of principle, to denounce almost all forms of sinus surgery. This unsettled state of affairs would seem to arise from — (1) lack of adequate routine study and evaluation of the sinuses in common clinical conditions, (2) lack of and slow diffusion of knowledge of sinus physiology and pathology, (3) lack of recognition by internists and rhinologists that many of their problems are mutual and require enlightened cooperation for their solution, (4) technical misconceptions and inadequacies.

The following are some of the symptom complexes we have seen associated with sinus disease in which it seemed reasonably certain to us that the sinusitis was a determining or aggravating factor: (1) Headaches acute and recurrent "nasal ganglion syndrome", (2) "Eye strain", (3) Lethargic states simulating typhoid, endocarditis, low grade sepsis, (4) Toxic conditions — athripsia, marasmus, debility, certain anemias, (5) Bronchitis, acute and chronic (occasionally misinterpreted as tuberculosis), bronchiectasis, lung abscess, (6) Allergic rhinitis, hay fever, (7) "Fog" states.

*Presented at the San Francisco Meeting of the American College of Physicians, San Francisco, April 5, 1932.

†From the Department of Clinical Research, University of Nebraska College of Medicine.

**The subject matter has to do almost entirely with chronic hyperplastic sinusitis. While acute empyema of one or more sinuses is not uncommon, empyema is quite often a suppurative phase of chronic sinusitis. Acute suppurative conditions must be handled conservatively. Time and observation will often decide whether a simple acute process or an acute suppurative phase of chronic hyperplastic disease is present.

asthenia, neurasthenia, mental disorders, (8) Focal complexes such as arthritis, myalgia, nephritis, myocarditis, neuritis, herpes, "colitis", etc; (9) The convulsif, spasmodic torticollis, "athetoid conditions".

Obviously sinus factors will be much more frequently diagnosed if they are suspected. Certain "leads" will be found useful in directing attention to the sinuses as a possible source of trouble, such as (1) Any of the sinusitis complexes mentioned above, (2) Facies "dull, puffy, weary eyes", "swollen nose and face", mouth breathing, nasal twang; (3) History of onset with a remote or recent "flu", with repeated colds, or following dental extractions, of undue sweating and chilliness, (4) History of chronic catarrh with nasal discharge or pharyngeal dripping; (5) Lateral pharyngeal lymphangitis, pharyngitis with visible mucoid, muco-purulent or purulent secretions in the nasopharynx; (6) Cervical adenopathy, especially of posterior chains.

The diagnosis of a sinus factor in systemic disorders should be made only after a complete clinical survey. The making of a diagnosis of a responsible sinusitis without the help of the rhinologist should be encouraged. It promotes independent thinking, prevents servile acceptance of "specialized" opinion, and helps to place the therapeutic decision on the shoulders of the general physician, where it belongs. It makes available advice based on the study of the patient as a whole. The fact that a chronic sinusitis is present is merely of interest, whether he who has the sinusitis suffers general ill health as a consequence of his sinusitis is another matter.

Roentgenology is by far our best objective method. The roentgenologist who takes pride in the accuracy of his positions, in the correctness of his exposures, and in the quality of his photographic work is a valuable ally. Opinions, even of highly trained and experienced roentgenologists, who are inclined to substitute interpretative skill and experience for poor films should be accepted with reservations. A word should be said for the use of a "scout" plate in the Waters position, even when there is little reason to suspect trouble. A normal film in the Waters position will go far toward ruling out a chronic sinusitis. If the clinical evidence still points to the sinuses a thorough rhinological examination with films in additional positions, with or without lipiodol, may be necessary. The general physician should acquire experience in film reading that his patient be not subjected to the liabilities of highly specialized interpretations. Finally, the platitude must not be forgotten that roentgenography reveals merely disturbances in densities and contour at a given time, and tells us little of the nature or behaviour of the pathological conditions present. The clinical records are often of more value than the ray findings. Occasionally repeated roentgenological studies are necessary to reach a decision. Such examinations are especially useful when allergic swellings of the sinus mucosae are in question.

Study and observation of the patient over considerable periods of time may be required. It may be necessary to follow his trouble through several recurring cycles in order to ascertain whether there is a hook-up between the patient's general and local symptoma-

There seems to be a lag in our knowledge of sinus pathology. There is little on the subject in the text books. The three volume English version of Kaufmann devotes less than a page to inflammatory disease of the sinuses. The sinuses are rarely investigated at autopsy and then only at the request of the clinician. Yet Harke¹ found 138 instances of gross inflammation of the paranasal sinuses in 395 autopsies. It would be interesting to see what change a routine postmortem exposure of the paranasal sinuses might work in our medical thinking on such subjects as lung abscess, méningitis, asthma, bronchiectasis, endocarditis, nephritis, and obscure septic and toxic conditions. In autopsies on deaths from asthma in which symptomatology referable to the upper respiratory tract is the rule, the sinuses have received scant attention. In the study of three cases of bronchial asthma with detailed postmortem analysis Kountz and Alexander² do not mention the sinuses. Huber and Koessler,³ in their well known analysis

Some of our lack of autopsy knowledge of paranasal sinus disease may be attributed to the want of any convenient method of exposure. The chisel is unsatisfactory and the sagittal head-splitting technique of Harke, although providing satisfactory exposures, gives most morticians a cold chill. One of us (F. L. D.) has devised a core drill fitted to a brace (figure 1) * The center drill is placed in the sella turcica and is directed in the midline and in the plane of the facial notches of the mandible (figure 2). The core (figure 3) brings out the sphenoids, the posterior ethmoids and part of the nasal cavities and turbinates, generally shears the mesial walls of the maxillaries and leaves the pharynx, tongue and tonsils exposed. By making a sagittal section of the core one will have had a complete exposure of all of the paranasal sinuses save the frontals and remaining ethmoids which may be easily opened through the orbital and ethmoid plates with a chisel.

*Arrangements have been made with
Medler and Company, Chicago, Ill., to
this code drill

pathology are based largely on material removed at operation. The process is considered to be an inflammation with epithelial hyperplasia. Eggston⁶ gives the following histopathological classification: (1) hypertrophic and polypoid, (2) atrophic or fibrotic, (3) mixed types. A better classification is that of Runge⁷ who considers chronic inflammation of the sinuses as chronic catarrhal and chronic purulent, both hyperplastic. The latter he sub-divides

into (1) an edematous or hypertrophic type, (2) a granulomatous or papillomatous type, and (3) a fibrotic type. It would seem that the various types described are merely different reaction patterns in the same pathological process. The multiplicity of pictures observed are conditioned by varying tissue responses to irritants, by the number, character and duration of acute infectious insults and by varying degrees of swellings and unswellings.

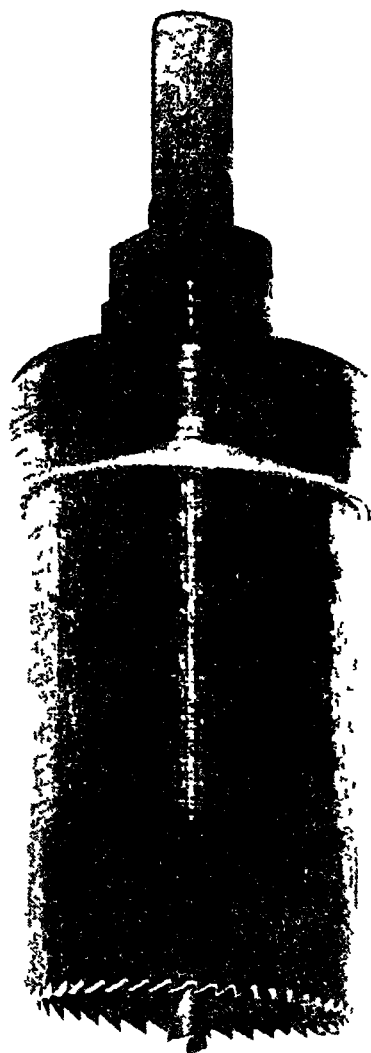


FIG 1 Core drill Two inches in diameter as used for average and large adults

which may profoundly change the reaction patterns in relatively brief intervals of time. One may obtain sections from a single sinus which run all the histopathological patterns described by various authors as different "types" of hyperplastic disease (Figures 4, 5, 6, 7). One of the most striking variations is in the water content. Wherry⁸ sees in tissue hydration a condition necessary for bacteria to invade the emulsion colloids of the body. In the abnormal variations in the water content of the mucous membranes may lie the

tendency in certain individuals to repeated upper respiratory infections. In this connection it is interesting to note that most hay fever patients ultimately develop a chronic sinusitis. Massive hydration and dehydration of the sinus mucosa accounts for the startling variations observed in allergic individuals by Proetz⁹ and others. Hydration factors and the high variability of the tissue reactions seen bring up the question of whether a pathological classification made on the basis of reversibility might not be more useful. As clinicians we

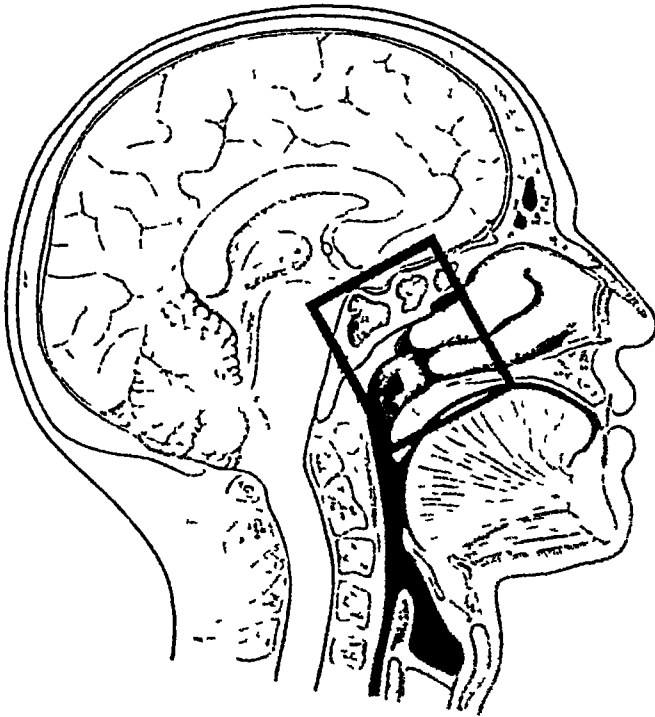


FIG. 2. Midsagittal schematic section of head showing area of interest for use and portion included in core. The core includes sphenoid, ethmoid, and the posterior nasopharynx, tissue of Rosenmüller posterior ethmoidal cells, portions of the soft and hard palate. On removing the core the maxillary sinus, tongue, pharynx, and back teeth are accessible.

are primarily interested in whether changes observed are fixed or relatively transient, whether changes revealed by roentgenograms with or without lipiodol or by endoscopy are reversible or irreversible, and what are the corresponding histopathological patterns. Such knowledge will ultimately determine the indications for conservative or radical methods of treatment.* In

*Correlation of results obtained by radical operation with the type of inflammatory reaction present in the tissues submitted has shown that favorable results are more likely the deeper the tissue infiltration, where the inflammatory reactions are superficial the process is quite likely to be a pansinusitis and belong to the allergic type. Fibrotic membranes are commonly associated with suppuration and are irreversible.

the problems of tissue hydration are involved the baffling interrelationships of asthma and upper respiratory infections. There is evidence that the answer to many of the bacterial asthmas will be found in chronic infections of the sinus mucosae.

It is unfortunate that we are forced to resort to pure morphological methods to identify bacteria in mucous membranes. Although rigorous precautions be taken to insure a sterile technic, deductions from cultures obtained from sinus membranes are open to the criticism of contamination. We have repeatedly found bodies in the deeper areas of tissues stained by the Gram method which in our opinion are diplococci (figure 8). Similar findings

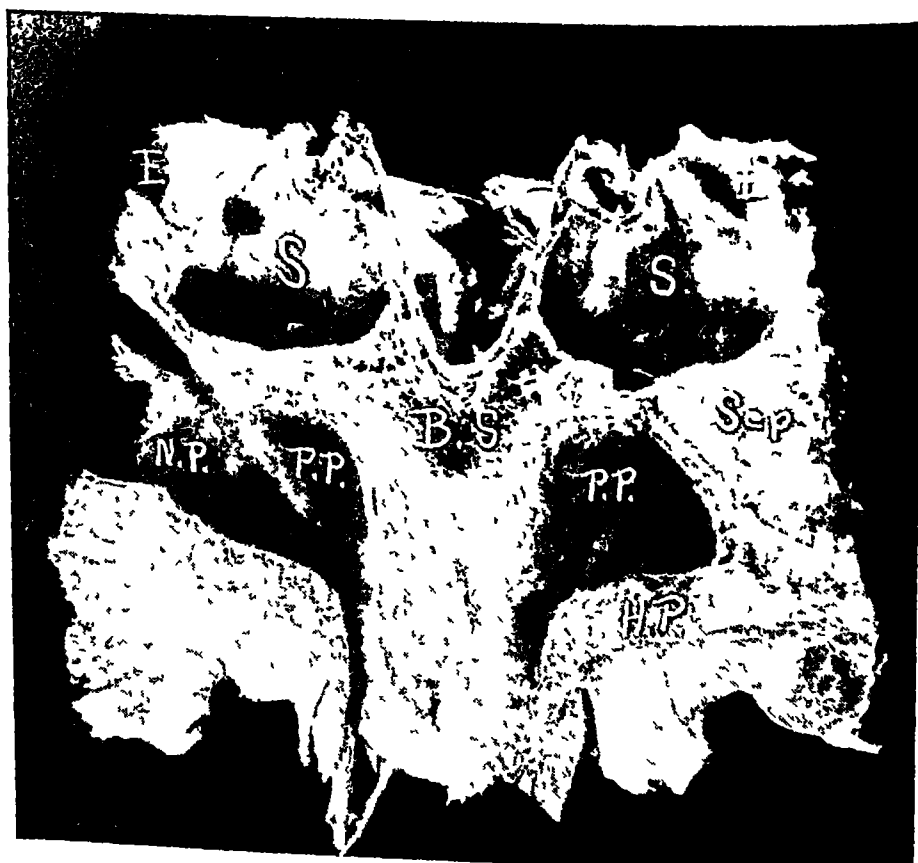


FIG 3 Core sawed open by sagittal cut
base of sphenoid P.P. = posterior pharynx S = sphenoid E = ethmoid B.S. =
N.P. = nasopharynx Sep = septum H.P. = hard palate

have been reported by others* 10, 11, 12

If pathogenic bacteria reside in diseased sinus tissues and find conditions more suitable to their growth in the deeper layers, obviously only those operative methods which accomplish a removal of the entire membrane should

*Cultures made with aseptic precautions from the mucosa of an asthmatic showed an organism in pure culture similar to those demonstrated later in the tissues. The cutaneous reaction to this organism was very sharp. The patient became immediately free from asthma following exenteration of his maxillary sinuses. Three months later a cutaneous reaction to the vaccine could not be obtained.

be considered in testing the focal infection theory as it pertains to chronic sinusitis. In analyzing our material the percentage of desirable clinical results was greater in those cases in which the material removed formed "casts" of the sinuses suitable for photographic reproduction (figure 9). When the specimens were badly torn or in fragments (figure 10) the follow-up showed a higher percentage of therapeutic failures. In other words, results were roughly proportionate to the degree in which an *en masse* removal of the diseased sinus mucosa was approached.

Chronic hyperplastic sinusitis as a

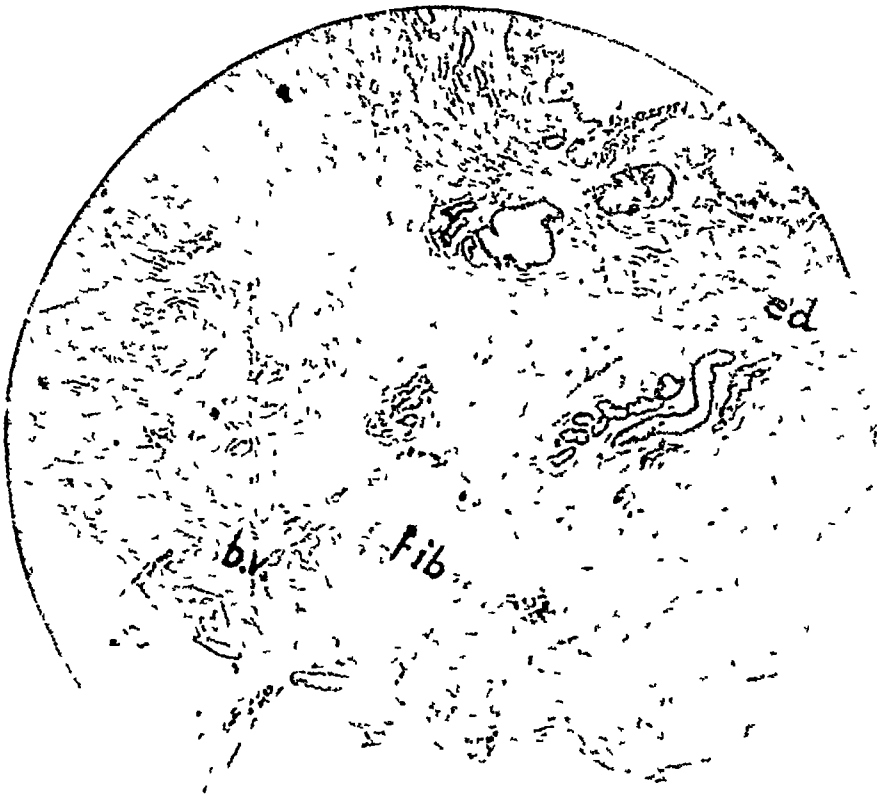


FIG. 4. Case no. V, V. H. Low power of portion of maxillary sinus showing various pathological processes which may be present in the deeper layers. ed = edema and hydrops; fib = fibrotic deeper layers; b.v. = blood vessels.

focus of infection has not been generally accepted. Some maintain that chronic (suppurative) sinusitis rarely if ever acts as a focus of infection,¹² others that it is not an uncommon source of systemic disease.¹¹ A partial explanation of such wide variance in opinion may well lie in the technic employed in treatment. Drainage of a sinus merely gives a sick membrane a better chance to get well by helping it to rid itself of its secretions. Drainage in no way eliminates the focus. Washing with antiseptic solutions should have about the same effect on a chronically infected mucous membrane as the same type of treatment might have

on chronically infected tonsils. Curettement of the mucosa should yield approximately the same results as curettement of tonsils, and it has been amply demonstrated that incompletely removed tonsils merely become greater liabilities from a focal infection standpoint. The validity of clinical experiments to determine the rôle of chronic sinusitis as a focus of infection hinges on a technic which will approach a bacterial excision of the focus. To strip intact diseased mucous membranes of varying degrees of friability from the walls of bony cavities of low accessibility requires the perfection of a surgical technic totally different from any hith-

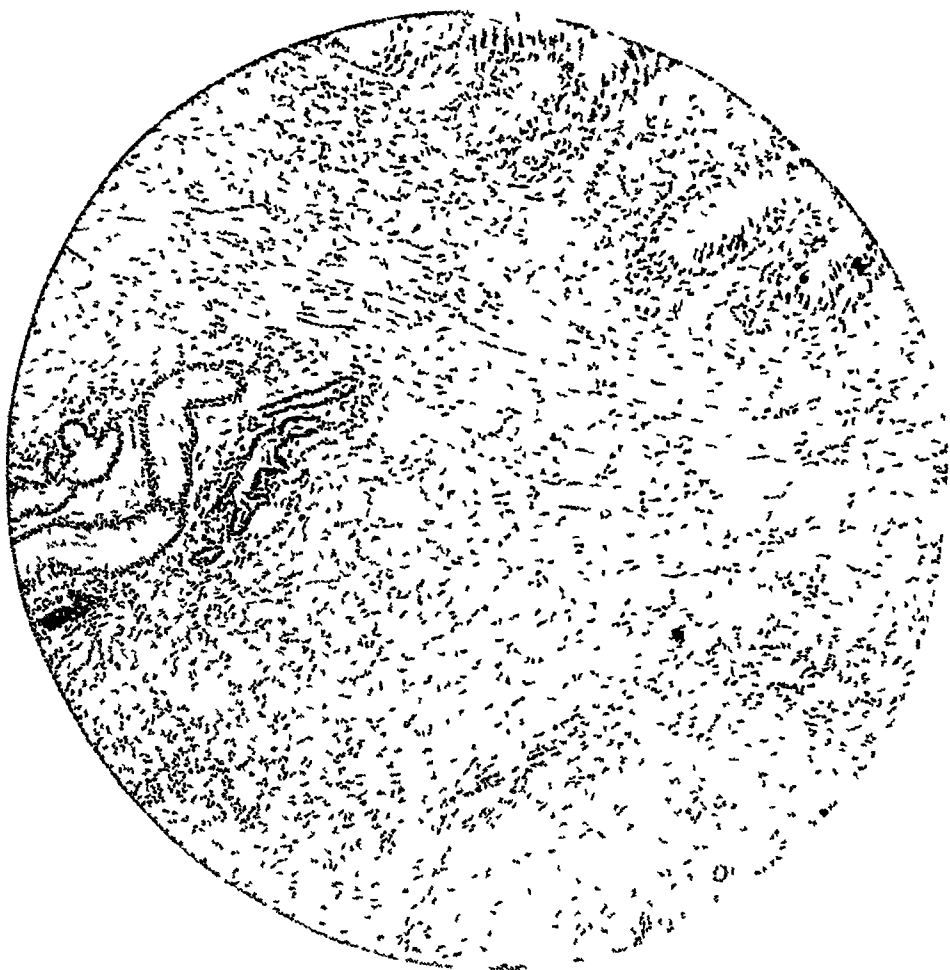


FIG 5 Case no. V. V. H. Higher power showing the hydrops and epithelial proliferation together with the inflammatory infiltration.

erto known Bacteriological, immunological, and pathological studies with animal inoculations will be helpful, but unless unanticipated methods be developed the solution of the problem of sinus infection in systemic disease in the final analysis will come from a statistical treatment of large series of clinical experiments, *the validity of which rests on rigorous diagnostic studies and a surgical technic which accomplishes an en masse excision of infected tissue with minimum trauma and without post-operative hemorrhage*

Results obtained in divers conditions such as chronic bronchitis, bronchiectasis, asthma, chronic arthritis, fag, nephritis, myocarditis, chronic heart

muscle insufficiency, low grade toxic states, etc, in selected cases, have convinced us of the focal possibilities of sinus disease Exenteration has been advised in patients whose troubles have been of some standing, who have undergone long and various treatments, and whose sufferings have been such as to make them willing to submit to any treatment that offered even a remote chance of success We have never advised exenteration in troubles of short duration, or where there seemed any likelihood of improvement by less radical methods Care has been taken to eliminate dento-alveolar sources of chronic sinusitis Removal of affected teeth and diseased bone by

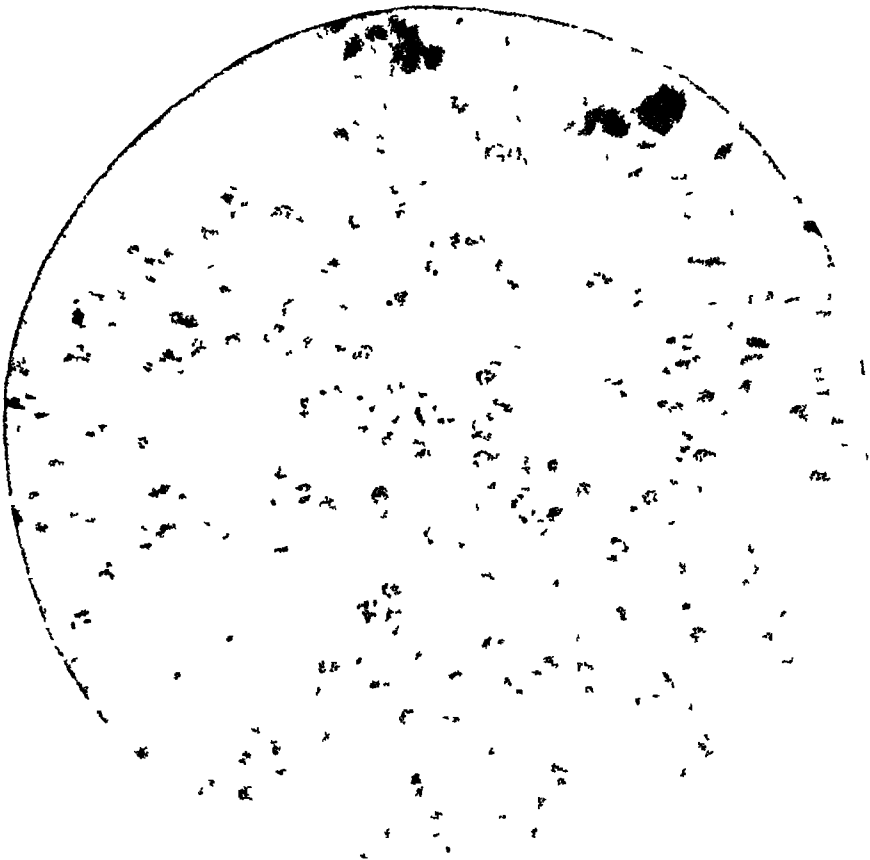


FIG. 6 Higher power of Section 3

alveolectomy^{15, 16} has been advised, letting the sinus mucosa alone if there seemed to be any reasonable chance of

*This operation, first devised by W. I. Shearer for cosmetic purposes, as developed and used by him is a highly satisfactory method for the removal of pathological conditions of the mouth. The mucoperiosteum is reflected from the alveolar processes and the teeth removed, all pathological tissues are exposed and removed "under the eye", the bony tissues are trimmed and smoothed, and the muco-periosteum trimmed and sutured. Healing is by primary intention. The "reactions" so common to other methods for the removal of teeth and mouth lesions are practically unknown. This method, when correctly applied, permits the removal of all lesions of the mouth at one sitting without fear of dangerous reaction. Twenty years

recovery from removal of the adjacent diseased tissue. Partial excision of the mucous membrane has been tried in a few instances with questionable results.

What we have said has been based largely on our experiences with chronic disease of the maxillary sinuses. The more nearly the condition has been confined to the maxillaries the better have been the results. The maxillaries are more accessible from both diagnostic and surgical standpoints. A larger mass of infected tissue can be com-

experience with this technic has convinced us that in proper hands it is the method of choice for removal of dento-alveolar foci of infection.



FIG 7 Fibrosis in deeper layers

pletely removed with less technical difficulty—a quantitative advantage. Satisfactory improvement occasionally follows maxillary exenteration in the face of involvement of the sphenoids and ethmoidal labyrinths—also a quantitative effect. We have made no studies of bone involvement described in connection with chronic sinusitis. Autopsy studies of this problem would seem pertinent.

The following brief abstracts from case records illustrate the results that may be obtained in favorable cases, and in which it seems reasonable to assume that the exenteration of diseased sinus mucosae has been a determining

factor in the patient's improvement or recovery. Failures have been present, especially in pansinusitis in patients in whom we have had reason to suspect that the exenteration has been incomplete, or when the systemic conditions seemed to have become fixed, when other variables have been present or the focal nature of the trouble questionable.

CASE REPORT

Case No 1 E S L, single, 19, entered the hospital March 25 1925, with a diagnosis of acute rheumatic fever and acute endocarditis. She gave a history of yearly recurrent attacks of acute rheumatic fever from the age of 5 until her tonsils were removed at 13. She was known to have a

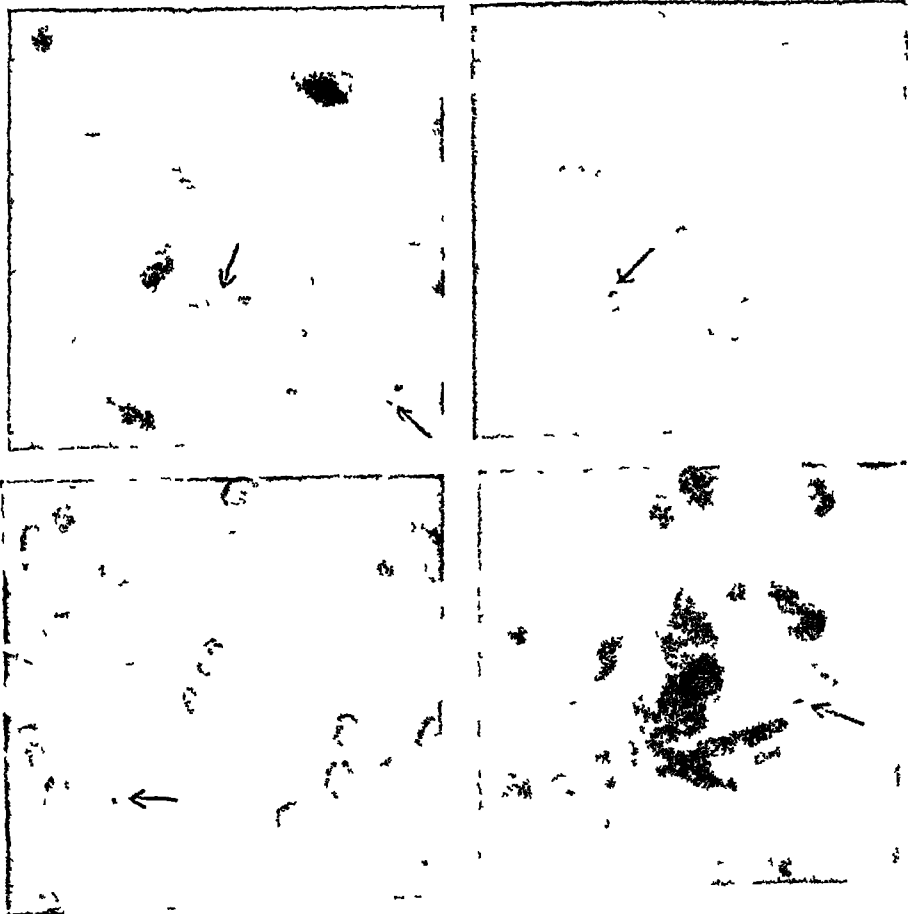


FIG 8 Diplococci indicated by arrows. (Giemsa stain.)



FIG 9 Case no VII, M C En masse exenteration of both maxillary sinus membranes Coronal section The material has been removed in one piece and the membrane is complete except for the usual tearing along the medial wall near the ostium



FIG 10 Exenteration of left maxillary sinus membrane by usual method Such material makes any opinion as to the completeness of the operation hazardous and suggests at least considerable trauma

damaged heart but her health had been reasonably good from that time until three weeks prior to her admission, when she contracted a cold, which was followed by a low grade fever. There was a profuse nasal discharge and she ached all over. Her knees became red, swollen and very painful, and she grew short of breath.

The physical examination showed a pale, young woman, orthopneic with acute rheumatic manifestations. The heart action was rapid. The apex was in the fifth interspace, 9 cm from the median line. The heart was 12 cm broad at the fourth interspace. From the heart findings a diagnosis of lesions at both mitral and aortic valves and of acute fibrinous pericarditis was made (the friction rub disappeared in 72 hours).

The urine examination was negative. The blood count showed a hemoglobin of 80, red blood cells, 4,200,000, leucocytes, 12,700. The Wassermann test was negative.

A remittant fever continued uninterruptedly for three weeks and on account of the history, rhinological and roentgenographic findings an attack upon the sinuses was decided upon in spite of the desperate condition of the patient.

Exenteration of the infected ethmoids and intranasal drainage of the maxillaries and sphenoids on both sides were done. Pus was found in both maxillary sinuses. Five days after the operation the temperature reached and held the base line. Convalescence was uneventful.

Comment. From the history, findings and clinical course one would have been justified in assuming an acute rheumatic or subacute bacterial endocarditis affecting previously damaged valves. Because there was a history of onset with an acute upper respiratory infection and clouding of the maxillary sinuses we decided to consider the sinusitis as a source of infection with or without a complicating acute or subacute endocarditis. On drainage of the infected sinuses a condition presumably of a precarious out-

look, became relatively benign. Serious re-infection, if any, of the endocardium had not occurred. The sinusitis was responsible for the febrile course. We have seen several similar cases and have come to consider the diagnosis of acute infectious endocarditis, even in the presence of obvious heart findings, as hazardous without excluding acute or subacute paranasal sinusitis. In the case under consideration we thought the sinusitis was of the acute suppurative type and the changes probably reversible. The patient has had no illnesses since, and would be considered a perfect physical specimen were it not for the valvular heart lesions. A Waters plate at the present time, however, shows hyperplastic membranes which were best removed as a preventive measure.

Case No. II. D. P., a young, married woman, age 23, was brought to the hospital July 27, 1929, with asthma, which had completely incapacitated her for the past six months. There was a history of repeated respiratory infections "pneumonia" at 4, 17, and at 19 when she was sick six weeks. The first attack of asthma had occurred in August, 1926. She had changed climate three times, elimination diets and protein tests had failed to reveal any allergic factors. Both maxillary sinuses were radiopaque. A clinical survey revealed nothing of significance except the signs of a chronic bronchitis with emphysema and a leucocyte count of 10,300.

Middle turbinectomy and radical exenterations of the mucous membrane of both maxillary sinuses were done. Both sinuses were filled with polypoid thickening and pus. The mucous membrane was decidedly fibrotic in type with marked vascular change. The epithelium was normal but in places atrophic. A large share of the specimen was sent for a corrective tissue study. The cultures of the diplococci were negative.

A report on Jan 30, 1932, states "I am in better health than since childhood I have had no bad attacks of asthma Once in a while if I run or exercise too hard in the cold I will "stuff up" for about 10 or 15 minutes At times when out in the cold or just before a storm my face hurts and I have pain between the eyes and in the cheeks" (probably ethmoid disease)

Comment This is a fairly well controlled case of severe intrinsic, incapacitating asthma, in which prompt and complete relief followed a radical exenteration of the diseased mucosae of both maxillaries Asthma patients should be studied from the standpoint of sinus infection either as a causative or a complicating factor. Severe cases, obviously intrinsic, with hyperplastic sinusitis should be given the benefit of the experiment of a complete exenteration, especially if the disease seems to be confined largely to the maxillaries After all, as Rackemann says, "It is infections that play havoc with our patients" which holds especially true of asthma

Case No III Mrs A A, age 70, had suffered from asthma for 20 years During the past two years the asthma had increased in severity until it had become incapacitating and life threatening on account of impending heart failure A careful history disclosed the fact that the onset of the asthma twenty years ago had been preceded by *extensive dental work involving devitalization of many of her upper teeth* Changes of climate and various dietetic, hygienic, and medicinal regimes had been instituted without benefit During the past two years her asthma had been practically constant and her condition had been made endurable only by the use of several hypodermics of adrenalin daily

The physical examination showed a poorly nourished, elderly woman, orthopneic and cyanotic The general physical examination revealed nothing further of marked import except a somewhat enlarged heart with a

slight systolic blow at the apex, various sized dry râles over the entire chest, slightly enlarged liver, and edema of the legs Rhinological examination yielded nothing of significance except tumefaction of the left inferior turbinate Radiograms in the Waters position showed moderately increased density in the floor of the maxillary sinuses, especially the left There was marked dento-alveolar disease throughout the upper jaw with obvious involvement of the floor of the left maxillary, and possible involvement of the right

Because the patient had suffered from asthma wherever she had lived and whatever she did, because diets had been tried and sensitization tests run by others, and because the onset of the asthma so closely followed devitalization of teeth twenty years ago, and because of such definite evidence of dento-alveolar and sinus disease on the left side, an alveolectomy with removal of the dento-alveolar disease and a Caldwell-Luc operation were done on the left side Feb 12, 1930 On account of the critical condition of the patient no work was done on the right Twenty-four hours after the operation the patient had her last hypodermic of epinephrin for that attack which had lasted unabated for six months

The patient is reported (March 20, 1932) as being relatively free from asthma although there has been some wheezing and shortness of breath on exertion

Comment The past two years have been relatively comfortable for this patient Contrary to advice the patient did not return to us for mouth work on the opposite side, but merely had the teeth extracted This patient illustrates the important relationship of dento-alveolar disease to chronic sinusitis and to asthma via the sinuses

Case No IV H M, farmer, aged 70, came under observation June 23, 1930 There was nothing of significance in the past or family history He stated that he had been quite well until three or four years ago when he noticed severe spells of coughing and shortness of breath associated with choking

spells nocturnal in type. During these times he had to be propped up in bed, for whenever he lay down he began to cough and choke. He said he had never had asthma and that he felt pretty well in the daytime but his nights were bad and dyspnea had been present on slightest exertion. There were no other symptoms of significance.

Examination showed a poorly nourished, elderly man, slightly cyanotic who choked up and coughed when he lay down. The following significant things were noted on the general examination: marked dento-alveolar infection, a moderately enlarged heart, pulse, 72, systolic blood pressure, 112, diastolic, 82, a systolic blow heard all over the precordium, musical in character and well transmitted to the axilla. There was no obvious evidence of heart failure.

Films showed very extensive alveolar disease with clouding of both maxillary sinuses, the latter corroborated by lipiodol filling defects. An electro-cardiogram showed low amplitude Q-R-S in all leads, conduction time normal, T-wave upright throughout.

Diagnosis. Extensive dento-alveolar disease, chronic hyperplastic sinusitis, asthma (?), chronic myocardial insufficiency.

Under observation in the hospital the attacks of dyspnea were largely at night and partook of the type of cardiac asthma. The urine examination was negative. Hemoglobin, 97 gms (56 per cent), red cells, 3,590,000, whites 15,000, 50 per cent polymorphonuclears. The Wassermann test was negative.

Double alveolectomy with exenteration of both maxillary sinuses produced a remarkable change in the patient's symptomatology.

Patient is reported (March 28, 1931) by his local physician as very active and reasonably well for a septuagenarian.

Case No. IV. V. H., age 16, consulted us on Jan. 3, 1930, for heart trouble. There was nothing of significance in the family or in the past history except tonsillectomy and adenoidectomy which were performed six years ago for repeated attacks of tonsillitis; there has been more or less constant catarrhal trouble for years, he has been subject to colds which have kept him out of school for weeks at a time.

Two years ago the patient had an upper

respiratory infection with bronchitis which "left his heart weak." Ever since that time he has been troubled with rapid heart action and palpitation. If he over-exercises his heart beats fast and he has a feeling of "being all in." He gets short of breath on going up hill. He also has pain and stiffness in the back at times. Recently every time he "gets bronchitis" his "heart is bad", and he has to stay in bed for weeks at a time.

The physical examination showed a well developed, well nourished lad. There was a pharyngeal lymphangitis and some enlargement of the posterior cervical glands. The tonsils were out and there was no evidence of mouth infection. The pulse rate lying was 88, sitting, 104, standing, 120. After 50 hops the pulse went to 142. One minute later it was 122 and five minutes after the 50 hops it was 106. There was no increase in the size of the heart and the sounds were normal. The systolic pressure was 135, diastolic, 85, temperature, 98.8°. There was no evidence of hyperthyroidism and the basal metabolic rate was -8. The physical examination was otherwise negative.

The urine examination was negative. The blood count was normal and the Wassermann test was negative. The electrocardiogram showed a rate of 90, R-wave upright in all leads, R-wave slurred in all leads, T-wave slightly diphasic in leads II and III. Sinus tachycardia, sinus arrhythmia.

Clinical diagnosis. Myocarditis, probably having origin in sinus infection.

A radiogram in the Waters position showed a large filling defect in the floor of the left maxillary sinus and clouding of the left ethmoids, graded ++. A rhinologic examination showed the septum deviated to the right, considerable hypertrophy of the middle turbinates, with swelling and enlargement of their posterior tips.

Operation. Bilateral in the upper part ethmoidectomy, radical left maxillary sinus drainage removal of middle turbinate, exploration of right maxilla.

Microscopically the tissue from the chronic infection of the maxillary sinus came out of the middle turbinate, the ethmoid and the septum. The tissue was almost entirely composed of inflammatory cells.

A report on Jan 30, 1932, states "I am in better health than since childhood I have had no bad attacks of asthma Once in a while if I run or exercise too hard in the cold I will "stuff up" for about 10 or 15 minutes At times when out in the cold or just before a storm my face hurts and I have pain between the eyes and in the cheeks" (probably ethmoid disease)

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spells nocturnal in type. During these times he had to be propped up in bed, for whenever he lay down he began to cough and choke. He said he had never had asthma and that he felt pretty well in the daytime but his nights were bad and dyspnea had been present on slightest exertion. There were no other symptoms of significance.

Examination showed a poorly nourished, elderly man, slightly cyanotic who choked up and coughed when he lay down. The following significant things were noted on the general examination: marked dento-alveolar infection, a moderately enlarged heart, pulse, 72, systolic blood pressure, 112, diastolic, 82, a systolic blow heard all over the precordium, musical in character and well transmitted to the axilla. There was no obvious evidence of heart failure.

Films showed very extensive alveolar disease with clouding of both maxillary sinuses, the latter corroborated by lipiodol filling defects. An electro-cardiogram showed low amplitude Q-R-S in all leads, conduction time normal, T-wave upright throughout.

Diagnosis. Extensive dento-alveolar disease, chronic hyperplastic sinusitis, asthma (?), chronic myocardial insufficiency.

Under observation in the hospital the attacks of dyspnea were largely at night and partook of the type of cardiac asthma. The urine examination was negative. Hemoglobin, 97 gms (56 per cent), red cells, 3,590,000, whites 15,000, 50 per cent polymorphonuclears. The Wassermann test was negative.

Double alveolectomy with exenteration of both maxillary sinuses produced a remarkable change in the patient's symptomatology.

Patient is reported (March 28, 1931) by his local physician as very active and reasonably well for a septuagenarian.

Case No. 17. V. H., age 16, consulted us on Jan. 3, 1930, for heart trouble. There was nothing of significance in the family or in the past history except tonsillectomy and adenoidectomy which were performed six years ago for repeated attacks of tonsillitis. There has been more or less constant catarrhal trouble for years. He has been subject to colds which have kept him out of school for weeks at a time.

Two years ago the patient had an upper

respiratory infection with bronchitis which "left his heart weak." Ever since that time he has been troubled with rapid heart action and palpitation. If he over-exercises his heart beats fast and he has a feeling of "being all in." He gets short of breath on going up hill. He also has pain and stiffness in the back at times. Recently every time he "gets bronchitis" his "heart is bad," and he has to stay in bed for weeks at a time.

The physical examination showed a well developed, well nourished lad. There was a pharyngeal lymphangitis and some enlargement of the posterior cervical glands. The tonsils were out and there was no evidence of mouth infection. The pulse rate lying was 88, sitting, 104, standing 120. After 50 hops the pulse went to 142. One minute later it was 122 and five minutes after the 50 hops it was 106. There was no increase in the size of the heart and the sounds were normal. The systolic pressure was 135, diastolic 85, temperature 98.8°. There was no evidence of hyperthyroidism and the basal metabolic rate was -8. The physical examination was otherwise negative.

The urine examination was negative. The blood count was normal and the Wassermann test was negative. The electrocardiogram showed a rate of 90, R-wave upright in all leads, R-wave slurred in all leads, T-wave slightly diphasic in leads II and III. Slight tachycardia, sinus arrhythmia.

Clinical diagnosis. Myocarditis, probably having origin in sinus infection.

A radiogram in the Waters position showed a large filling defect in the floor of the left maxillary sinus and clouding of the left ethmoids graded -3. A rhinological examination showed the septum deviated to the right, considerable hypertrophy of the middle turbinates, with swollen and inflamed tips of their posterior tips.

Operation. Bilateral alveolectomy, ethmoidectomy, radical tonsillectomy, adenoid removal, mucous membrane exploration of the nasal cavity.

Microscopically the myocardium showed chronic diffuse interstitial myocarditis, consisting of the replacement of the myocardium by connective tissue and a moderate inflammatory reaction. The inflammatory reaction was composed of lymphocytes and mononuclear cells.

Chronic fibrous sinusitis, irreversible with little possibility of recovery by other than radical measures

Comment Rapid improvement followed the operative attack. At the end of two years the patient was well. He has had only occasional colds and no cardiac symptoms. The rapid cessation of symptoms and the resumption of growth and development on the part of this boy following the radical removal of the sinus infection has been striking. It is reasonable to assume that we were dealing with myocardial damage, either toxic, or from myocarditis due to actual bacterial invasion of the heart muscle, and that the focus was in the sinuses.

Case No VI F R H, farmer, aged 51, consulted us Jan 23, 1930, because of "fag". The patient had enjoyed good health until three years prior when he began to have attacks characterized by weakness, loss of appetite, soreness across lower abdomen, slight fever, a yellow sallow color and unaccountable sweating. During these attacks, which were often precipitated by changes in weather, he ached all over and there was some chilling. There has been no nausea, vomiting, excessive gas or constipation, nor mucus in the stools. These attacks have been growing in frequency and have been gradually incapacitating him. There was no history of tonsillitis or repeated upper respiratory infections. The past and family histories were of no importance and there was little history of catarrh.

The patient was a well developed, middle aged man, with a dirty, sallow, subicteric hue. He seemed exhausted. His skin was wet. The tonsils were adherent, the anterior pillars red, and pus could be expressed from the left one. There was no particular enlargement of the submaxillary glands. There was a lateral pharyngeal lymphangitis, especially on the left, but no enlargement of the posterior cervical lymphatic glands or of the thyroid. The

examinations of the heart, lungs, abdomen, rectum and nervous system were negative.

A Waters plate showed the right maxillary sinus fairly clear, left clouded (graded +3), frontals and ethmoids apparently negative. A rhinological examination showed mucopurulent secretion in the left nares and swelling of the left middle turbinate. Films of the teeth showed dento-alveolar disease and an unerupted molar on the right side, residual pathology and a partly erupted molar on the left, and probable involvement of the floor of both maxillary sinuses, especially left.

Diagnosis Focal infection with two obvious foci, tonsils and dento-alveolar disease with a left chronic hyperplastic maxillary sinusitis secondary to periapical disease.

The tonsils were removed, Jan 7, 1930. No improvement followed. Bilateral alveolectomy with resection of polypoid masses from floor of left maxillary sinus was done on Feb 20, 1930. The mucosa of the right maxillary sinus appeared approximately normal and was not resected. An x-ray film in the Waters position showed a normal left maxillary sinus shadow on April 9, 1930. During the early summer the patient felt some better but his improvement was not satisfactory. There was a return, however, of the old trouble with loss of weight, sweating, and increased fatigability in September, 1930. In December, 1930, he had a severe attack with headache, aching all over and fever up to 101°. Recently he has had a cough. There has been no pain in head, but patient feels as if he were "taking cold" with chilling at night, there has been a great deal of nasal discharge.

Rhinological examination (Jan 7, 1931) showed very definite evidences of sinusitis. A Waters' plate showed the right antrum with opacity graded +1, left, +2. Lipiodol showed considerable thickening of mucosa of right maxillary sinus and a marked filling defect of the left. Stereoscopic plates of the chest revealed nothing but the peribronchial infiltration usually associated with a chronic sinusitis. Intravenous cholecystography showed a normally functioning gallbladder.

Diagnosis Chronic hyperplastic sinusitis of both sides, recurrent on left. On Jan 14, 1931, bilateral Caldwell-Luc operations with *en masse* removal of mucosae of both

maxillary sinuses were done. The left maxillary sinus was half filled with thickened mucous membrane with polypoid hyperplasia. A pocket of pus was found in the mucous membrane in the anterior-inferior portion. The right antrum showed the same type of membrane as the left but with pus filling the entire cavity.

The patient reported well on March 23, 1931.

Comment. This patient presented an obscure diagnostic problem, infectious in origin. After removal of the tonsils without improvement, bilateral alveolectomy with removal of polypoid masses from the left maxillary brought some improvement with a normal left maxillary sinus shadow. Recurrence of the chronic hyperplastic sinusitis with polypoid masses in the left and with suppuration on the right necessitated radical procedures. A satisfactory recovery followed exenteration of both maxillary sinuses.

Case No. VII. M. C., widow, age 46, consulted us on June 19, 1930. There was nothing of significance in the past or family histories.

Present Illness. The patient had enjoyed excellent health until December, 1928, when she had influenza and was in bed five days. Her nose was stopped up, she had fever and severe headache. She had had some catarrhal trouble previously but it became much worse afterwards. Since then she has never been well. A tonsillectomy was performed, and three abscessed teeth were removed in July, 1929. The only result was a rapid increase in her weakness. In September, 1929, she was taken with terrific pains in the stomach and bowels, and was unable to sleep or eat for which she was hospitalized. Since then there have been more or less abdominal distress and insomnia. She has had night sweats. She has been constipated and forced to take almost daily cathartics. Her chief complaints were extreme weakness, pain and distress in the abdomen, headache, especially on the right side, with a sensation of pres-

sure and a feeling of fullness and ringing in the ears. She has been hospitalized three times since the onset of her trouble undergoing a rest cure and treatment of 12 weeks' duration for mucous colitis.

The physical examination showed a poorly nourished, tired appearing woman with a woe-begone, neurasthenic facies. The abdomen was diffusely tender with sharply localized tenderness without rigidity in the right lower quadrant. Otherwise the physical examination revealed little of importance. The urine examination was negative. The blood count was—hemoglobin, 12.3 gms (Newcomer), red blood cells, 3,980,000, white cells, 6,400, polymorphonuclears, 60 per cent, mononuclears, 40 per cent. The blood Wassermann test was negative. The gastro-enterological examination was negative except that the appendix did not fill with barium, the right lower quadrant of the abdomen was tender, and the colon was spastic. A rhinological examination showed no evidence of paranasal sinus trouble but a Waters' plate revealed changes in density which were confirmed by lipiodol.

On account of the possibility of a chronic appendicitis the patient was hospitalized for observation and placed on a smooth-anticonstipation regime for three weeks with little improvement in the abdominal symptoms. Radical excision of the mucosa of both maxillary sinuses was performed on July 8, 1930, (figure 9) and was followed in four months by a normal state of health. Both antra were practically filled with polypoid thickened mucous membrane. Multiple abscesses containing thick yellow pus were found in the mucosae.

The patient reported herself well on September 17, 1931.

Comment. This patient is of interest from several standpoints. (1) A text book case of (neuro) asthenia may be associated with a sinus infection. (2) Typical mucous colitis with abdominal pain, spastic constipation, may be complicated and cured following removal of a sinus focus of infection. (3) The diagnosis of this case is

was made entirely on the clinical record with the help of roentgenograms. Examinations by two rhinologists without films brought back a report of "no material evidence for paranasal sinus pathology"

SUMMARY

1 A brief statement of sinusitis as a general medical problem has been attempted

2 Three postulates for a valid clinical answer to the question of chronic sinusitis as a source of systemic disease may be laid down, viz — (1) rigorous diagnostic surveys, (2) a technic which accomplishes a bac-

terial excision of the infected tissues, and (3) statistical studies of series of cases which satisfy the first two postulates

3 A core drill, which should help in promoting routine post-mortem examination of the sinuses has been described

4 Abstracts from the clinical records of a few illustrative cases, with comments, have been presented

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REFERENCES

- ¹RUNGE, H G Die entzündlichen Erkrankungen der Nase, Handb d spez path Anat u Hist, (Henke u Lubarsch) 1928, Bd III, Erster Teil, J Springer, Berlin, 132
- ²KOUNTZ, W B, and ALEXANDER, H L Death from bronchial asthma, report of three cases, Arch Path, 1928, v, 1003-1019
- ³HUBER, H L, and KOESSLER, K K Pathology of asthma, Arch Int Med, 1922, xxx, 689-760
- ⁴MARCHAND, F Ein neuer Fall von Asthma bronchiale mit anatomischer Untersuchung, Deutsch Arch f klin Med, 1918, cxxvii, 184-209 Huber and Koessler, 1c
- ⁵WRIGHT, C B Death from bronchial asthma, Jr Am Med Assoc, 1930, xciv, 1218-1221
- ⁶EGGSTON, A A The pathology of chronic sinusitis, Arch Otolaryng, 1930, xii, 561-584
- ⁷RUNGE, H G Die entzündlichen Erkrankungen der Nase, Handb d spez path Anat u Hist, (Henke u Lubarsch) 1928, Bd III, Erster Teil, J Springer, Berlin, 137-145
- ⁸WHERRY, W B Tissue hydration and its relation to susceptibility and immunity as shown by skin tests in asthma, chronic sinusitis, and other infections, Jr Infect Dis, 1927, xli, 177-189
- ⁹PROETZ, A W Displacement method in sinus diagnosis and treatment, its advantages and limitations, Tr Am Laryng Assoc, 1930, lxi, 121-140
- ¹⁰WATSON-WILLIAMS, P Remarks on tissue invasion of low grade pyogenic microorganisms, Jr Laryng and Otol, 1929, xlii, 598-600
- ¹¹JONES, N W, and KISTNER, F B Chronic sinus infection in relation to systemic disease, ANN INT MED, 1931, iv, 752-771
- ¹²ROSENOW, E C Personal communication
- ¹³ANDERSON, C M Suppuration in paranasal sinuses as a factor in focal infections, review of 400 cases, Jr Am Med Assoc, 1930, xciv, 1889-1891
- ¹⁴JONES, N W, and KISTNER, F B 1c
- ¹⁵DUNN, A D, and SHEARER, W L Some application of the principle of focal infections with a method of removal of extensive disease of the alveolar processes, Minn Med, 1920, iii, 241
- ¹⁶SHEARER, W L External alveolectomy, Jr Nat Dent Assoc, 1920, vii, 499-504

The Local and Constitutional Pathology of Bronchial Asthma*†

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G RIMM,¹ in 1925, found but thirty cases of bronchial asthma with autopsy findings and microscopic studies. Since that time, nine additional cases have been recorded by Rackemann² (one), Kountz and Alexander³ (three), Dehner⁴ (two), Steinberg and Figley⁵ (two), and Wright⁶ (one). Of this total number of thirty-nine cases, careful studies have shown² that many of the cases earlier reported were not true bronchial asthma, while in not more than twelve cases can death be said to have resulted directly from asthmatic paroxysms. Huber and Koessler,⁷ in their monograph upon the subject in 1922, presented only four cases from the literature (amongst twenty-one), and one of their own series (number 2), in which death resulted from a seizure of bronchial asthma. The remaining fatal cases are gathered from the above authors, Kountz and Alexander having the largest series of three deaths, although Rackemann reports having attended five patients in whom death was apparently due solely to an asthmatic seizure, but autopsy was not performed.

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Collected from 3,690 autopsies at the Hospital of the University of Michigan since 1896, is the following series of eight cases, in five of which death can be laid to asphyxia or cardiac failure during, or immediately following a paroxysm of bronchial asthma.

In this study, attention has been paid particularly to the pathology of the individual structural layers and units of the bronchi and peribronchial tissue. For two reasons no attempt has been made to determine absolute measurements of bronchial wall thickness. (1) Many apparent fallacies render this procedure of uncertain value. The most important source of error is the wide variation in the activity of individual units of the bronchial excretive system—mucous epithelium, glands, blood vessels and capillaries. Furthermore, it is evidently quite impossible to obtain a comparable series of cross sections of bronchi from any two individuals, dependent as they are for accuracy upon the distance from bifurcations (cartilage-plaque thickness) and individual variations in structure and the varying states in which the normal submucosal and muscular layers may be found postmortem as well as upon technical artifacts. (2) In spite of these difficulties, Huber and Koessler⁷ and later, Kountz and Alexander³

were able to show quite definitely, by painstaking measurements of the bronchi of asthmatics and non-asthmatics, a thickening of the bronchial walls as a whole at certain levels, and of the individual layers, in the asthmatic individual. The uniformity of results obtained by these investigators makes certain the fact that the bronchial thickening seen grossly and microscopically, is not only apparent but real. For present purposes, then, the bronchi are divided relatively into those of small, intermediate, and large orders, those of intermediate size ranging from 2 to 5 mm in outside diameter. They were studied with reference to their respective layers, recognizing the epithelial mucosa (with goblet cells), basement membrane (upon which the former rests), subepithelial layer, musculature, glands, fibrocartilaginous layer, variable lymphoid tissue, and the vascular and nerve supply.

It is proposed not only to correlate the clinical and pathological findings in this series, but to view such results in the light of the theories of etiology in vogue at the moment. In particular, the proof for that type of asthma known as "bacterial" will be questioned. An effort will be made to review the anatomic findings in these cases with the hope of finding indications of some basic factors in the predisposition (if such there be) of the individual to allergic phenomena in general.

CASE REPORTS

Case I (Path No A-I-AI) O S, a male aged 43 years, was first a patient in the University Hospital in April, 1930, and subsequently returned for further treatment towards the end of June of that year. For five years he had suffered from attacks of paroxysmal dyspnea, increasing in frequency

and severity, and accompanied by a cough which at times was productive of a small amount of yellowish sputum. The dyspnea was inspiratory in type. The relief obtained from epinephrin was inconstant. With the periodic lessening of a chronic nasal discharge would come headaches, and more frequent and severe attacks of asthma. A thirty-pound loss in weight during the preceding year and occasional malleolar edema were noted.

Clinical and laboratory studies showed evidence of pansinusitis, nasal polypi, slight leucocytosis, a blood eosinophilia of 13 per cent, and an inconstant hypertension, as well as the classical physical signs of bronchial asthma. Sensitization tests showed positive reactions for hemolytic and nonhemolytic streptococci, and micrococcus catarrhalis from stock vaccines. Sputum culture yielded a hemolytic streptococcus, *Streptococcus viridans*, and *Micrococcus catarrhalis*. From these cultures vaccines were prepared, with which positive sensitization reactions were shown to a nonhemolytic streptococcus and *Micrococcus catarrhalis*.

During his stay in the hospital the patient was observed in many asthmatic attacks. Some were so severe as to give the impression of impending death. Such attacks resisted the administration of epinephrin, atropine, nitroglycerin, morphine, and magnesium sulphate, while those of less severity responded to the use of epinephrin. The nasal polypi were removed during April. In June the autogenous vaccine was given for a short time in repeated small injections, but during this procedure the attacks became so severe that the course had to be discontinued. On several occasions it had been noticed that severe attacks of asthma had followed the administration of coal tar products. On July 1st, one-half hour after taking 0.6 gm. of aspirin, the patient suffered a severe attack of asthma, in the midst of which death occurred, evidently from respiratory failure. Artificial respiration was of no avail although the heart sounds were audible for twenty-five minutes after the cessation of respirations.

Autopsy was performed nine hours post mortem. The body was that of a well developed, emaciated white male, 162 cm. in

length The thorax was not remarkable on external examination Upon removal of the sternum, the lungs ballooned out into the incision in close approximation A marked dilatation of the right heart was noted The right ventricular wall measured 8 mm in thickness, of which one-fourth was composed of fat The tricuspid valve admitted three fingers, and the pulmonary valve two Both valves appeared normal The left ventricular wall measured 20 mm in thickness The mitral and aortic valve orifices were of normal size The mitral valve, near the attachment of the chordae tendineae, presented indurated, nodular thickenings, and adjacent endocardial sclerosis No gross areas of fibrosis were noted The heart as a whole measured 14 by 10 by 5 cm, and weighed 280 gms The left lung measured 25 by 17 by 7 cm, and weighed 300 gms, while the right lung was 23 by 19 by 8 cm, and weighed 310 gms

The lungs were extremely voluminous Both apices presented rather firm adhesions The lungs were fully air-containing throughout, of uniform spongy consistency They cut with markedly increased resistance Both parietal and cut section surfaces were mottled slate gray in color, with some reddish coloration in both lower lobes posteriorly The large bronchi gaped widely, with evident thickening of their walls The smaller bronchi contained mucous plugs resembling tenacious jelly, and adherent in many places to the bronchial walls The trachea and main bronchi showed redness and swelling of the mucosa, with slight amounts of mucinous exudate

Further gross examination revealed no notable findings Blood culture at autopsy gave a growth of *B. pyocyanus* and *B. coli* The Kahn procedures, both diagnostic and presumptive, were negative.

Microscopic Examination Localized thickenings of the leptomeninges were noted with one area of active infiltration Most notable in the heart was a patchy fibrosis of the myocardium, with atrophy and hypertrophy of the heart muscle Endocardial sclerosis of long standing, and advanced atherosclerosis of the coronaries were additional features Small latent syphilitic lesions were present in the aorta

In general, the lungs showed a well marked emphysema, with numerous small patches of fibrosis Areas of chronic passive congestion were noted The terminal bronchioles and smaller bronchi were dilated and some of them contained plugs of laminated mucus Even the small bronchioles showed a hyalinization of the basement membrane The changes in the bronchi of intermediate size, however, were more marked A majority of these showed laminated and stratified mucus filling the lumen and constituting Curschmann's spirals The lumina were somewhat dilated, and showed frequent small saccular extensions, some of which were produced by the widening of the mouths of mucous glands The bronchi of this order also showed marked cellular infiltration of the wall which was characteristically eosinophilic and which in many areas pervaded the muscle There was only a moderate degree of hypertrophy of the muscular layer in the bronchi, but a very distinctly hyaline basement membrane The large bronchi showed changes practically of the same character as those of intermediate size. The hyaline basement membrane was wide and prominent The eosinophilic infiltration extended to the cartilages, and in some instances occurred in the connective tissue on the parenchymal side of the cartilage plates There was a chronic bronchitis

The bronchial nodes showed lymphoid hyperplasia with lymphoid exhaustion The thyroid gland was deficient in colloid with microscopic evidence of Graves' constitution In accord with the persistent hyperplastic thymus the adrenals were hypoplastic and all lymph nodes hyperplastic with exhaustion of the germinal centers In the pancreas were seen areas of interstitial pancreatitis Atrophic gastropericardial diffuse toxic fatty infiltration of the liver, and an early arteriosclerotic nephropathy were the only additional noteworthy findings

Case Summary A 45-year-old male who had "bacterial asthma" for five years, treated with autogenous vaccines, became so tired worse under their use that they had to be discontinued About three weeks before death

sensitive to coal-tar products, he died in a paroxysm of asthma following the ingestion of a therapeutic dose of aspirin. The significant local pathological findings were (1) Hyalinization of a thickened basement membrane throughout; (2) most marked pathology in the bronchi of intermediate size, (3) occlusion of lumina by exudate, (4) eosinophilic infiltration, (5) sacculations of the bronchi, (6) moderate hypertrophy of the muscular layer.

Case II (Path No A-38-AI) S T, 75 years of age, was admitted to the Department of Internal Medicine in the University Hospital on September 3, 1930, and expired less than 36 hours thereafter. In the short history obtained, all details typical of attacks of bronchial asthma were related. These had their origin, evidently, eight years previously when working in a munition factory. There he inhaled large amounts of acid fumes, and soon began to suffer from asthmatic attacks. Latterly, suffering from constant orthopnea and dyspnea, with frequent daily paroxysms of asthma, he was admitted as an emergency after a tiring journey from his home in a distant part of the state. During the short time he was under observation, he passed from one asthmatic attack into another. A few hours after admission, his temperature was 102°, with a leucocytosis of 27,000. Signs in the chest were obscured by the intense asthma present. Twenty-four hours after admission, the patient became cyanosed, with marked tachypnea, and shortly thereafter lapsed into coma. In spite of appropriate measures, he died a few hours later.

Autopsy was performed 16 hours post mortem. The body was that of an asthenic white male, 183 cm in length. Malleolar edema was present. The thorax was flat but symmetrical, the costal angle greater than a right angle. Both pleural cavities contained about 25 cc of clear colorless fluid. There were a few adhesions, posteriorly, of each lung to the thoracic cage. The lung borders were 1 cm apart in the an-

terior mediastinum. The cardiac apex was found to be at the sixth rib in the anterior axillary line. Thymic tissue could not be seen. The heart measured 15 by 12 by 7 cm, weighed 375 gms, and appeared globular in shape, with the apex formed mainly by the left ventricle. The left ventricular wall measured 2½ cm in thickness, without gross evidence of fibrosis. Both mitral and aortic valve orifices were of normal size, with the mitral cusps showing a slight sclerosis. The right ventricular wall averaged 6 mm in thickness, one-sixth of which was fat. The ventricle was dilated, the musculature relaxed and flabby. There was slight relative insufficiency of the tricuspid and pulmonary valves.

The left lung measured 27 by 17 by 7 cm, and weighed 600 gms. The organ was markedly emphysematous. The lower lobe presented a sharply circumscribed area of bronchopneumonia. Throughout, the bronchi showed many mucous plugs blocking the lumina, and the bronchial walls showed very marked thickening. The right lung, weighing 820 gms, measured 26 by 21 by 6 cm, and presented essentially the same changes as its neighbor, with a slightly larger area of bronchopneumonia in the middle lobe. Here also the bronchi of intermediate size were thickened and filled with mucous plugs. The bronchial glands were enlarged and anthracotic. The spleen presented several small, calcareous nodules. Some perigastric adhesions were noted. In the right lobe of the thyroid was an adenoma of 15 mm diameter.

Microscopic Examination A slight myocardial atrophy and fibrosis, endocardial sclerosis and lime salt deposit in the base of the valve cusps constituted the lesions in the heart. In conformity with these changes were the aortic atherosclerosis and calcification.

In addition to an acute purulent bronchitis with acute fibrino-purulent lobular pneumonia, the lungs showed uniform emphysema and an acute exacerbation of a chronic passive congestion. The smaller bronchi were uniformly dilated, and without hypertrophy of their respective layers, or hyalinization of the basement membrane. In both the large and intermediate bronchi, but most

evident in those of large caliber, was seen hypertrophy of the musculature. In both of the latter classes of bronchi the predominant change was a thickening and hyalinization of the basement membrane. This varied in degree, and could not be said to be more prominent in one or the other class. Filling many of the larger bronchi were spirally twisted masses of mucin and fibrin (Curschmann's spirals). The bronchial outline was rendered irregular and somewhat sacculated by dilatations between the muscle bundles, and at many points this seemed to have been accomplished by taking advantage of the mouths of the mucous glands. A marked cellular infiltration about both the intermediate and larger bronchi included numerous eosinophiles. The pulmonary arteries presented a well marked proliferation of the intima, without hyaline change. There was a chronic adhesive pleuritis. In the bronchial nodes were seen, in addition to anthra-

cosis, numbers of rather recent epithelioid tubercles, without caseation. The trachea also presented a marked hyaline change in a thickened basement membrane under which were infiltrating large numbers of eosinophiles. There was, in addition, an active chronic purulent tracheitis.

A proliferating adenoma of the thyroid was accompanied by atrophy and increased stroma of the gland, with calcification of the thyroid arteries. In the spleen were several encapsulated calcareous tubercles. On the inferior surface of the liver the capsule was thickened, and there was a proliferation of the small bile ducts in the capsule, with brown atrophy of the parenchyma.

Case Summary The asthmatic condition in this case apparently had its origin in exposure to acid fumes and lasted eight years in a man aged 75 at

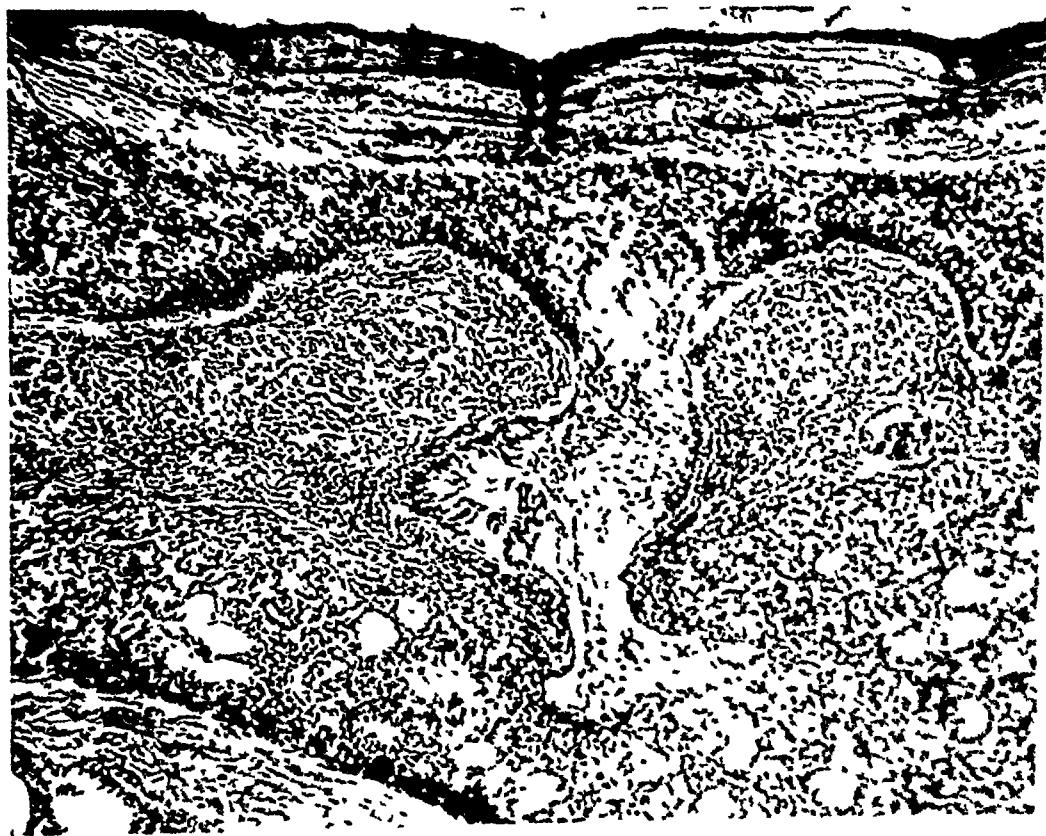


FIG. 1. Case II. Wall of large bronchus with hypertrophy of the musculature, thickening of the mucosa. Hyaline thickening of basement membrane. Sacculated dilatation of the bronchus. Mucous gland passing between muscle bundles.

death The terminal condition was that of extreme exhaustion brought on by repeated, successive seizures, on which was superimposed an acute fibrinopurulent lobular pneumonia The significant findings were (1) Hyalinization of a thickened basement membrane, (2) muscular hypertrophy most marked in the larger bronchi, (3) sacculations of the bronchi, (4) occlusion of many bronchi by exudate, (5) eosinophilic infiltration, and (6) mucous glands fairly prominent

Case III Z H (Path No A-122-AH), a male of 53 years of age, machinist, claimed that until eight months before his admission to the University Hospital in October, 1929, he had been without cardiorespiratory or other symptoms of ill-health Following an attack of influenza in the spring of 1929, periodic seizures of bronchial asthma appeared, usually nocturnal So rapidly progressive had been the course of the illness, with frequent seizures, constant dyspnea, anorexia, emaciation, asthenia, and profound general depression that in three months' time he had ceased to work and became a semi-invalid Admitted after two weeks of almost constant dyspnea and productive cough, it was found necessary to administer adrenalin or ephedrin every three hours for the control of the constantly recurring paroxysms In spite of such medication and the addition of morphia, the asthmatic attacks became more severe, and three days after admission death occurred during a particularly severe paroxysm, the patient having passed through six attacks during the previous twelve hours Laboratory studies showed seven per cent blood eosinophilia and many eosinophiles in the sputum

Autopsy The lungs were extremely voluminous, ballooning outwards when the sternum was removed Only a few apical adhesions were present on the right side There were no areas of consolidation or infarction, and no evidence of a purulent process Section revealed a striking emphysema Many of the bronchi contained plugs of mucoid, gelatinous material Grossly, there

was no notable bronchial wall thickening The lungs weighed 410 and 460 gms The thymus persisted as two well-defined lobes, each one of which measured 8 by 1½ by 1 cm The heart measured 14 by 9 by 7 cm, and weighed 335 gms The right ventricular wall, entirely muscular, measured 1 cm in thickness, with very marked right cardiac dilatation

Microscopic Examination In the heart there was a marked fatty change, subepicardial fatty infiltration, and subendocardial degenerative fatty infiltration The hyoplastic heart muscle showed a well marked brown atrophy, and there was an endocardial sclerosis of slight degree Except for the chronic passive congestion, emphysema, and numerous heart lesion cells, all the findings in the lungs centered about the bronchi The terminal bronchioles were moderately dilated In the bronchi of all degrees, but most marked in those of intermediate size, stood out a marked hyaline thickening of the basement membrane There was, however, only a slight hypertrophy of the bronchial musculature, most evident in the bronchi of intermediate size The eosinophilia was notable, infiltrating the bronchial muscle to some extent, but most striking in the bronchial lymph nodes The medium sized, and a few of the larger, bronchi showed sacculations, some of which were quite deep, each extending through an hiatus in the musculature, but with the thickened basement membrane always intact Many of the sacculations had their origin at the mouths of the mucous glands, which were quite prominent In some areas in the cartilage there was slight eosinophilic infiltration, but no destruction In many small bronchi there were plugs of fibrin and desquamated epithelium, while many of the medium-sized bronchi contained Curschmann's spirals An acute fibrinopurulent bronchitis was noted The thymus was persistent and hyperplastic with fatty atrophy

Case Summary An asthma of sudden onset such as this, occurring in a 50-year-old man, and following influenza, may be accepted as "bacterial" in origin After only eight months'

duration in which the disease fairly overwhelmed him, death occurred in an attack at the end of three days spent in the hospital, during which time he had been almost continuously in asthmatic orthopnea. The significant pathologic findings were (1) Marked hyaline thickening of the basement membrane, (2) slight hypertrophy of the bronchial musculature, (3) marked eosinophilia, seen also in the bronchial lymph nodes, (4) extensive sacculations, (5) partial occlusion of many lumina by exudate, (6) prominent mucous glands.

Case IV L. B. (Path No. A-306-AG), a 58-year-old farmer, was under observation in the medical service of the University Hospital from May 21, 1929, until his death on June 12 of that year. His chief complaint was of vague gastric distress, and secondarily of asthmatic attacks, chiefly nocturnal, for two years. Physical signs in the chest were typical of bronchial asthma. The blood eosinophilia was 12 per cent. Sensitization tests were not done. Evidence of upper respiratory infection, or of accessory nasal sinusitis, was lacking. During his stay in the hospital the patient had almost nightly severe asthmatic paroxysms, which but infrequently responded to ephedrin and adrenalin. On the day of his death he developed a severe asthmatic attack, which resisted the most heroic measures of medication, and he died after practically two hours' continuous asthmatic dyspnea.

Autopsy was performed three hours after death. On each side the diaphragm was at the level of the sixth rib. The lungs were voluminous. The thymus was well represented by fatty remains. The heart measured 13 by 10 by 4 cm. and weighed 280 gms. with a left ventricular wall thickness of 17 cm. The right heart moderately dilated showed subepicardial fatty infiltration. The lungs had a combined weight of 600 gms. and presented a striking emphysema. The thickened bronchi stood out from the cut surface with obvious narrowing of their

lumina. Apart from congestion no other changes were noted except for a moderate, generalized atherosclerosis. A culture from the heart's blood showed no growth.

Microscopic Examination The atrophic myocardium showed degenerative fatty infiltration, and there was marked subepicardial fatty change. The most marked features in the lungs were the extreme emphysema and the narrowing of the medium-sized bronchi. This latter was accomplished by infolding of the mucosa in irregular fashion, creating longitudinal rugae of varying heights. The mucosa, always intact, was thick, and beneath it there was a markedly thickened, hyalinized basement membrane present in bronchi of all orders. The intermediate bronchi showed further a thick, cellular subepithelial layer with but a slight eosinophilic infiltration. The musculature was markedly hypertrophic, but in an irregular fashion, interrupted at many points. The mucous glands were not prominent. At no point was there any marked eosinophilia. A few of the large bronchi contained granular mucinous material in small amounts with desquamated epithelium. Chronic purulent bronchitis and chronic passive congestion were the only other findings of note in the lungs.

Case Summary No evidence can be adduced in this case as to the etiology of the condition. Sensitization tests were not carried out, but none of the findings clinical or pathological indicate a focus of bacterial infection. In spite of the age of the patient and the short duration this case can best be attributed to an allergic factor. The following are significant pathologic findings: (1) Parasternal cysts, (2) medium-sized bronchi, (3) markedly thickened hyalinized basement membrane, (4) hypertrophied bronchial musculature, (5) granular exudate in the bronchi, (6) eosinophilia, (7) a moderate emphysema, (8) epithelial layer.

Case V M C (Path No A-123-AG), was a 36-year-old construction foreman who gave a definite history of asthmatic attacks occurring almost daily from 1914 up to the time of admission to the University Hospital in April, 1928. At this admission studies pointed to a "bacterial" bronchial asthma, and he was discharged with autogenous vaccines made from the strains of *B coli* and *Staphylococcus albus* to which he had shown positive sensitization tests. Readmitted in November, he reported that during the vaccine injections, the asthmatic attacks had become more frequent and more severe. The physical signs of bronchial asthma were present during both admissions. Blood eosinophilia was nine per cent. There was no definite evidence of sinus infection. Asthmatic paroxysms were frequent and severe during the second admission, with orthopnea even between the attacks. There were two to four attacks daily, responding

generally to the administration of adrenalin. On the day of death the patient passed from one paroxysm to another for six hours.

Autopsy The thorax was emphysematous in type. The heart measured 13 by 11 by 6 cm, weighed 345 gms, and showed a terminal right-sided cardiac dilatation of marked degree. The lungs showed a widespread and advanced emphysema with an area of atelectasis in the left lower lobe. The thickened bronchi stood out prominently and contained mucoid exudate. At the right base there was seen one small area of bronchopneumonia, not purulent. Mediastinal and bronchial nodes were hyperplastic.

Microscopic Examination The heart showed only extensive fatty changes. The lungs, apart from the bronchi, showed chronic passive congestion, emphysema, patches of dense fibrosis, an old area of organizing fibroid pneumonia, and one area of recent purulent lobular pneumonia. The



FIG 2 Case V Medium sized bronchus with marked hyaline thickening and folding of the basement membrane. Spiral plug of tough mucus in lumen. Marked chronic catarrh.

bronchial pathology was shown particularly by the bronchi of intermediate size, although the terminal bronchioles, in spite of dilatation, presented a marked hyaline change in the basement membrane, and the larger bronchi were thickened without the same accentuation of the basement membrane. The bronchi of medium size showed varying changes. In many the mucosa was thrown into folds of such height as to cause marked narrowing, but always with continuity of the well-marked, thickened and hyaline basement membrane except where pierced by the mouths of the mucous glands, others showed sacculations of considerable depth, and in these the mucous glands were distinctly hypertrophic. In some areas the bronchial lumina were filled with mucoid, homogeneous masses not of the Curschmann type, and poor in cells. The muscular hypertrophy was variable—quite marked in some bronchi, and almost negligible in others. A few small ulcerations of the bronchial mucosa were noted. The bronchial eosinophilia was quite striking, but there was no eosinophilia in the bronchial nodes. The main bronchi were notable in that they showed a marked hyaline change in a thickened basement membrane which extended also about the mucous glands. The thymus was hyperplastic. The liver showed healed miliary tubercles, and the gastrointestinal tract a chronic catarrh. An early arteriosclerotic atrophy of the kidney was present.

Case Summary. This case of 14 years' standing and said to be bacterial in origin was aggravated by the attempts to establish immunity to the supposedly offending organisms. Death occurred as a direct result of repeated seizures. The findings of interest are (1) Thickening and hyaline change of the basement membrane, (2) the varying changes in the intermediate bronchi, (3) exudate in the bronchial lumina, mucoid and homogeneous (4) small ulcerations of the bronchial mucosa, (5) marked bronchial eosinophilia.

Case VI (Path No A-91-AI) The first admission of R. B., a 13 year old girl, was to the Pediatric Service of the University Hospital in February, 1930. Her chief complaint was 'asthma'. A paternal grandmother had suffered from hay fever. Whoopingcough and chickenpox were the only events in the patient's medical history. Since early childhood there had occurred frequent asthmatic attacks with cough and sputum. She was quite ill on admission, with marked dyspnea, musical râles throughout the chest, and no consolidation. During her stay in the hospital, she developed a lobar pneumonia with subsequent empyema, which was drained by rib resection in April. Having been discharged towards the end of May, the patient was readmitted in September for recurrence of the asthmatic attacks. During this admission the thoracic sinus became healed. She was observed in many typical asthmatic attacks. Sensitization tests were positive for a large number of animal substances, food proteins and bacteria. The attacks of asthma became more frequent and more distressing during October with an alarming increase in her previously marked asthenia. On October 18 intratracheal lipidol injection was done, radiographic study showing slight enlargement of the right lower bronchi but no definite bronchiectasis. Following the lipidol injection the patient complained of extreme nausea and vomited several times. She became cyanosed with gradual diminution of pulse pressure, and respiration ceased on the following day about 20 hours after the injection.

Autopsy. The thorax was opened showing on the right side a sternotomy 5 by 2½ cm. well-healed scar over the eleventh rib. The lungs were extremely congested and edematous. The right pleural space was filled with exudate by adhesions which prevented any aspect of heavy consolidation. The tracheostomy wound was healed. There were present on the posterior surface of the right lung a few small nodules of white fibrin. No definite consolidation was seen in the right lung. The left lung measured 7 by 4 by 3 cm. and weighed 100 g. entirely normal. The heart measured 22 by 15 by 5 cm. and weighed 100 g.

Congestion and edema of the lung parenchyma were noted. The small bronchi showed moderate dilatation, the larger bronchi hypertrophy, and the lumina of the latter a tenacious, mucoid exudate. The right lung was slightly smaller in volume, 18 by 12 by 8 cm, but weighed 740 gms and showed marked edema. In the main bronchus was found a tough fibrinous membrane forming a complete cast extending into the bronchi of the second order. In the intermediate bronchi were found many plugs of mucoid exudate, while the smaller bronchi were dilated. In the larynx and trachea the mucosa was covered with a mucopurulent exudate.

Microscopic Examination Atrophy of the heart was apparent, with Zenker's necrosis, fatty degenerative infiltration of the myocardium and relative increase in stroma. The aorta was hypoplastic, the pulmonary artery, slightly atheromatous. In general, the lungs showed chronic passive congestion with an acute exacerbation and edema. Curschmann's spirals were present in many of the bronchi. The bronchi of intermediate size showed the most marked thickening of the bronchial wall, especially muscular hypertrophy with eosinophilic infiltration. Hyaline thickening of the basement membrane in the bronchi of all sizes, even those of less than 1 mm outside diameter, was marked. The large bronchi were without the same degree of thickening presented by those of medium size. Superimposed on these changes was an acute purulent bronchitis and a hyperplasia of the mucous glands. Both in the bronchial lumina and throughout the lung were numerous oil droplets which had not given rise to any reaction. The bronchial nodes were infiltrated with eosinophiles. Except for hypoplasia of the adrenals equivalent to that of the aorta, there were no other notable findings.

Case Summary This child had suffered from asthmatic attacks for many years and it should be noted that sensitization tests, carefully carried out, indicated that she was hypersensitive to several types of allergens. In conformity with this, it is a reasonable con-
 jec-

ture that her death was due to an allergic reaction to lipiodol. Of note in the pathologic findings are: (1) A marked hyaline thickening of the basement membrane comparable to that found in the preceding cases; (2) distinct muscular hypertrophy in the bronchi of medium size; (3) distinct eosinophilic infiltration of the bronchial walls and of the lymphnodes, (4) hyperplasia of the mucous glands.

Case VII S K (Path No A-343-AH), a white male of 56 years of age was first admitted to the University Hospital on April 25, 1930. His chief complaint was 'asthma', which was of three years' standing, and the onset of which he attributed to the forced inhalation of fumes from the spraying of lacquer paint in the factory where he was working. With the asthma there occurred swelling of the face and feet, palpitation, and two months later, hay fever, which was shown by sensitization tests to be due to ragweed. Two sinus operations were followed by pneumonia which confined him to bed for 14 weeks. A course of 'injections' was given with no benefit. The hay fever recurred each summer, the asthma, palpitation and edema became worse as time went on, and there were frequent attacks of abdominal colic. In the family history, the mother had had asthma, while other immediate relatives had suffered from rheumatic conditions, tuberculosis, and cancer. When admitted the patient was extremely weak, in an asthmatic (cardiac?) condition, but during his stay in the hospital he suffered many typical asthmatic paroxysms. The blood eosinophilia was six per cent. Acute abdominal pain was a frequent complaint, for which no cause was determined. A rapidly developing pneumonia in the right lower lobe caused death on May 8, 1930.

Autopsy The body was dolichomorphic in type, with evidence of recent loss of weight and the appearance of premature senility. The lungs were voluminous, filling the anterior mediastinum, and the cardiac apex was at the level of the fifth rib, inside the midclavicular line. The heart, except for

some atherosclerosis of the aortic cusps, and terminal right-sided cardiac failure, was not remarkable. The lungs together weighed 1260 gms, the right lower lobe showing practically complete consolidation. The left lung, extremely voluminous, presented marked thickening of the bronchial walls, which projected above the cut surface of the organ. Splenic, hepatic, mesenteric and peritoneal tubercles of varying ages were found.

Microscopic Examination The heart, in addition to subepicardial fatty change, showed marked endocardial sclerosis and fibrosis extending into the myocardium. The coronaries were markedly sclerotic, without obliteration. Extensive areas of croupous pneumonia in the right lower lobe showed partial organization of the fibrinous plugs in many alveoli. The emphysema was patchy and there was an acute exacerbation of a chronic passive

congestion. All of the bronchi showed the changes characteristic of bronchial asthma. The medium-sized bronchi in particular had a hyaline basement membrane of unusual thickness. Most of the bronchi were filled with a tough mucin. There was an irregular folding of the mucosa of each of the bronchi as well as many sacculations which not infrequently passed entirely through the musculature at the mouths of the mucous glands. The bronchial musculature was very hypertrophic, and in a remarkably uniform fashion. The eosinophilic infiltration was less marked than that seen in the other cases with the same degree of alteration of the mucosa, and there were no eosinophiles in the bronchial nodes. Acute purulent bronchitis and areas of bronchopneumonia completed the pulmonary pathology. In the bronchial nodes were encapsulated, caseating tubercles. Generalized atherosclerosis ar-



FIG. 3. Medium sized bronchus with hyaline thickening of basement membrane and a localized area of metaplasia of epithelium to columnar type. (H. & E., 100X). Changes characteristic of bronchial asthma.

teriosclerotic nephropathy, and fibroid atrophy of the testes were noteworthy findings

Case Summary This case resembles number II of the series in that the onset of the asthma was attributed to the inhalation of chemical fumes, with the subsequent establishment of a diagnosis of hay fever on a protein-allergic basis occurring at intervals, concomitantly with the asthma. As a further contribution towards possible etiology is the record of two (evidently) radical sinus operations. Further should be noted the 19 weeks' illness with 'pneumonia' and the absence of benefit from 'injections'. Pathological features of interest are (1) An unusually thick, hyaline basement membrane, (2) the presence of mucosal foldings, as well as many sacculations, (3) marked uniform hypertrophy of the bronchial musculature, (4) slight degree of eosinophilia, (5) mucinous exudate in the bronchi, (6) hyperplasia of the mucous glands

Case VIII S A (Path No A-142-AG), a 58-year-old white female admitted to the Gynecology service of the University Hospital in 1927 for vaginal bleeding, had suffered from asthma since the age of 13. She had had pneumonia at least four times. The asthmatic attacks had increased in frequency in the preceding few years. In 1928, following irradiation for a pelvic neoplasm at intervals during the year, she returned to the hospital critically ill and died in a few hours.

Autopsy There was a remarkable facial hypertrichosis, although the body hair was normal in distribution and amount. Lung borders were 2 cm apart in the anterior mediastinum. Areas of lymphoid tissue were apparent in the thymic fat. The heart presented a distinct relative right-sided preponderance (right ventricular wall, 11 mm thick, left, 17 mm), and a terminal right-

sided failure. The lungs showed purulent bronchopneumonia. There was an apparent increase of fibrous tissue along the bronchial tree and many of the bronchi were dilated. There were adenomas in the thyroid gland. In the body of the uterus there was a sloughing, neoplastic mass with much scar tissue adjacent to it.

Microscopic Examination Diffuse fatty change and endocardial sclerosis were seen in the heart with slight localized fibrosis of the myocardium. The lungs showed an acute purulent bronchitis with acute purulent bronchopneumonia. In areas there was a marked hypertrophy of the bronchial epithelium, amounting in places to a metaplasia to a stratified type. Quite as prominent as this was the almost universally thickened and markedly hyalinized basement membrane. The bronchial lumina varied widely in configuration—some quite regular, others presenting extensive sacculations, often through the musculature, but always with continuity of the basement membrane. The subepithelial layer was moderately thickened. All the bronchial lumina were widened. The muscular layer was distinctly hypertrophic. In none of the bronchi, or any of the lymph nodes, was there any degree of eosinophilia. The greater part of the body of the uterus was replaced by a peritheliomatous angiosarcoma, probably arising in a leiomyoma.

Case Summary The interest in this case lies in the duration of the disease—45 years. The age of onset and the absence of foci of infection would indicate that this case did not belong to the class of bacterial asthmas. In view of the long standing pulmonary disease, the following are of interest: (1) Marked hypertrophy of the bronchial epithelium, (2) universally thickened and markedly hyalinized basement membrane, (3) distinct hypertrophy of the bronchial musculature, though not greater in degree than in some of the preceding cases, (4) extensive sacculations of the bronchi; (5) moderate thickening of the subepithelial layer;

- (6) widening of all the bronchial lumina, (7) absence of eosinophilia

DISCUSSION

From a clinical viewpoint in each of these eight cases the criteria of bronchial asthma were established. Five of them died from the immediate results of asthmatic paroxysms. In the last three cases the cause of death was intercurrent infection or neoplasm, thus making possible a contrasting study with those in which the asthmatic phenomena were predominant at death. The duration of the disease in this series of cases varied from eight months to 45 years, the age of the patient from 13 to 75 years. According to the classi-

fication still employed clinically cases I, III and V would be termed 'bacterial' while cases II, IV and VIII probably conform to the negative appellation of one writer—'non-bacterial allergic asthma'. In the remaining two cases sensitization tests and clinical evidence make it clear that the individual was not only hypersensitive to certain allergens but also had foci of infection usually accepted as being of paramount importance in 'bacterial' asthma.

The clinical evidence of bronchial asthma and its periodic dramatic crises with which the older writers were mainly concerned are too well known to bear repetition. It should be re-



FIG. 4. Medium sized bronchus in case of bronchial asthma. The wall of the smooth muscle in the wall. Extensive inflammatory cell infiltration. Many of the cells at this point are eosinophils.

teriosclerotic nephropathy, and fibroid atrophy of the testes were noteworthy findings

Case Summary This case resembles number II of the series in that the onset of the asthma was attributed to the inhalation of chemical fumes, with the subsequent establishment of a diagnosis of hay fever on a protein-allergic basis occurring at intervals, concomitantly with the asthma. As a further contribution towards possible etiology is the record of two (evidently) radical sinus operations. Further should be noted the 19 weeks' illness with 'pneumonia' and the absence of benefit from 'injections'. Pathological features of interest are (1) An unusually thick, hyaline basement membrane, (2) the presence of mucosal foldings, as well as many sacculations, (3) marked uniform hypertrophy of the bronchial musculature, (4) slight degree of eosinophilia, (5) mucinous exudate in the bronchi, (6) hyperplasia of the mucous glands

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Autopsy There was a remarkable facial hypertrichosis, although the body hair was normal in distribution and amount. Lung borders were 2 cm apart in the anterior mediastinum. Areas of lymphoid tissue were apparent in the thymic fat. The heart presented a distinct relative right-sided preponderance (right ventricular wall, 11 mm thick, left, 17 mm), and a terminal right-

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DISCUSSION

From a clinical viewpoint, in each of these eight cases the criteria of bronchial asthma were established. Five of them died from the immediate results of asthmatic paroxysms. In the last three cases the cause of death was intercurrent infection or neoplasm, thus making possible a contrasting study with those in which the asthmatic phenomena were predominant at death. The duration of the disease in this series of cases varied from eight months to 45 years, the age of the patient from 13 to 75 years. According to the classi-

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The clinical evidence of bronchial asthma and its periodic dramatic crises with which the older writers were mainly concerned are too well known to bear repetition. It should be re-



FIG 4 Medium sized bronchus from case of bronchial asthma, showing hypertrophy of the smooth muscle in the wall. Hyaline thickening of basement membrane and cellular infiltration. Many of the cells in this infiltration are eosinophiles.

marked, however, in support of the statement of Huber and Koessler,⁷ that the coincidence of blood and sputum eosinophilia is pathognomonic of the disease, pulmonary distomiasis and hydatid disease alone excepted

Constitutional Pathology

In reviewing the gross and microscopic findings in these cases, one is impressed by certain constantly recurring evidences of constitutional pathology. These center about the lymphoid apparatus and the chromaffinic and vascular tissues. Table I (p 272) shows the remarkable manner in which all these cases conform in essential detail to the state known as the thymico-lymphatic constitution. Many of these cases, in spite of the fact that all had reached middle age except one child of 13, showed well-defined thymic remains even grossly, while all but one showed microscopic evidence of general lymphoid hyperplasia. Every case presents hypoplasia of the adrenals and of the aorta. As to physical habitus some of these patients were of the asthenic dolichomorphic type of the thymico-lymphatic constitution while others were of the gouty-arthritic habitus.

Local Pathology

Dealing with the local pathological changes, the microscopic features of the bronchial and peribronchial tissues are of the greatest interest. Most constant are those occurring in the basement membrane. In this series, variable as it is in respect to apparent etiology, age of the patients, and duration of the disease, the basement membrane changes are striking in their uniformity. These are two in number,

thickening and hyalinization, as first noted by Monckeberg.⁸ Which is primary cannot be said with certainty, for both are well marked in the case of only eight months' standing. Always marked in the intermediate bronchi, these changes may extend into the smallest bronchioles, and in certain instances are most extreme in the large bronchi. The absolute and unvarying continuity of the membrane changes no matter how extensive the sacculations, or how high the mucosal rugae, is a matter of note. For many years this basement membrane change has been recognized in this laboratory as an invariable finding in asthmatic conditions. How advanced this change may become is illustrated by case V, of 14 years' standing, in which the thickened and hyaline basement membrane in the main bronchi extends even about the mucous glands (figure 2). This case is also of interest in showing small ulcerations of the bronchial mucosa—a finding previously noted by Kountz and Alexander³ and Berkart.⁹ In the other case of long duration (number VIII, 45 years), the epithelium presents a marked hypertrophy. Increased cellularity has led to some increased thickness of the subepithelial layer in practically all the cases, but is most evident in case IV. In this layer the eosinophilia, when present at all, is generally most prominent.

Second only to the basement membrane change in constancy, is the hypertrophy of the bronchial musculature. That the degree of hypertrophy is not proportionate to the duration of the disease is shown by the fact that case IV two years after onset has the most marked muscular hypertrophy which

far outshadows that seen in case VIII after 45 years of asthma. In accord with this is the finding of only an irregularly distributed muscular hypertrophy in case V of 14 years' duration, while case III after eight months presents a uniform hypertrophy of slight degree. It is therefore quite evident that some other factor or factors must enter into the mechanism of the asthmatic orthopnea.

Einthoven¹⁰ first proved (1892) by experiments later duplicated by Brodie and Dixon¹¹ (1903), that stimulation of the peripheral end of the vagus in itself was sufficient to produce stenosis of the bronchi, due to a contraction of the muscle fibers. Dixon further found that the same phenomenon occurred in a decerebrate animal by irritation of the nasal mucous membrane. In 1909 Monckeberg⁸ first noted histologically an hypertrophy of the bronchial musculature in an asthmatic, and this, together with Auer's statement¹² that the anaphylactic process takes place in animals in which the vagus nerves had been cut long enough to produce degeneration of the nerve endings, not only enabled Meltzer¹³ to explain asthma on the basis of allergy, but apparently vanquished those proponents of the "mucosal edema" theory of bronchospasm, who stressed the activity of the bronchial exudative system (*Vide* Faschingbauer,¹⁴ Unverricht¹⁵). In the experimental animal, peripheral vagal stimulation doubtless produces preeminently a spasmodic contracture of the bronchial musculature, but the analogy to the asthmatic state is only apparent, and modified by many other factors, intrinsic and extraneous. Experimental proof is not lacking that vagal stimu-

lation produces in addition vasodilatation, and that the nerve carries secretory fibers to the bronchial glandular system. In the asthmatic individual on an allergic or other basis, with the chronicity of the condition, and probably some degree of chronic infection superimposed, it is apparent that the neurogenic substrate is much altered as compared to the experimental animal. With this much evident, reference to cases III, IV, V, and VIII makes it apparent that the histopathology taken in correlation with the clinical course of these cases substantiates the suggestion of Alexander¹⁶ that the bronchoconstriction is in reality due to a combination of all the effects of peripheral vagal stimulation, namely muscular contraction, vasodilatation, and glandular secretion, with one or the other assuming the dominant rôle in the individual case. The argument as to the respective importance of the muscular contraction and the "mucosal edema" is therefore quite pointless.

In conformation with this is the varying degree of hyperplasia and prominence of the mucous glands. In case IV, which presented the most marked muscular hypertrophy, the glands were atrophic.

The frequency of tissue eosinophilia in asthma has long been recognized, and the nature of the eosinotactic stimulus a point of controversy. In five cases of this series the eosinophilia was a notable feature, its absence in two of the remaining three is possibly to be accounted for by the presence of superimposed predominant pulmonary infection which overshadows the asthmatic process. The degree of eosinophilic infiltration was highly variable. Several

cases showed infiltration of the bronchial musculature and, to a slight degree, even of the cartilage, but in none was there the erosion and destruction of cartilage noted by certain observers.³ The subepithelial layer contained the largest number of eosinophiles, but they may be spread outside the cartilage and be prominent in the peribronchial tissues. In cases III and VI the bronchial lymph nodes were remarkably infiltrated. Clinically, the blood eosinophilia is a most constant feature in this series, ranging from six per cent to thirteen per cent. One author,⁵ in attempting to differentiate the histopathology in "bacterial" and "non-bacterial allergic" asthma, has made the claim that eosinophilia is practically absent in the former, and constant in the allergic type. All three of the present cases that could be considered "bacterial" showed a marked eosinophilia, even infiltrating the muscle and bronchial nodes in case III, while case IV, which was without suggestion of bacterial etiology, showed only a slight eosinophilia although dying in an asthmatic crisis.

Although founded on the postulates laid down by such observers as Virchow, Marchand, and Ribbert (perivascular lymphoma), the conception of true autochthonous tissue eosinophilia cannot be accepted. The massing of the eosinophile cells varies in location from subepithelial to peribronchial layers, may be absent at some points, occurs in the bronchial nodes, and in the spleen and thymus (Huber and Koessler), and in some cases the eosinophiles can be seen in great numbers about the bronchial capillaries. Schlecht first proved (1910) that blood eosinophilia occurred regularly

as part of the anaphylactic process upon reinjecting sensitized animals. Recently Unverricht¹⁵ drew attention to the fact that Schilling has proved definitely the production of eosinophiles in the bone marrow, their entrance into the blood stream, and their mobilization in the lungs from the blood in the anaphylactic animal. Moreover, the eosinophiles were found to disappear wholly from the circulating blood at the onset of the anaphylactic seizure, subsequently reappearing and becoming more numerous. Upon extirpation of the spleen or its exposure to x-ray, the eosinophiles in the circulating blood were increased, whereas, conversely, the injection of splenic juice caused a reduction of the blood eosinophilia. The eosinophilic increase, then, in the circulating blood and tissue is most reasonably regarded as a generalized hematopoietic response, designed for protection against the foreign allergic substance, be it bacterial, peptone, amine or chemical, but acting as an eosinophilotactic stimulus. Its absence is generally due to some superimposed infection which assumes dominance, and in response to which the leukopoietic function is altered. This has recently been proved by the work of McGregor on experimental sinus infection in animals, in which the introduction of a fresh infection caused the complete disappearance of eosinophiles from the tissues in a relatively short time.

In the guinea pig dead from an anaphylactic shock, the classical picture in the lung fields is the almost absolute stenosis of the bronchi due to obliteration of the lumen by infolding of the epithelium and contraction of the muscular layer. This has never

been exactly duplicated in man, although in one case reported by Boughton,¹⁷ dying after the injection of 1 minim of horse serum, the microscopic picture in the lungs was very similar to that seen in the sensitized guinea pig. The opposite, however, is seen in most of the reported cases, as in this series, in which the most frequent finding is extensive sacculation interrupting the continuity of the muscular layer and extending through the mouths of the mucous glands, the latter evidently offering the necessary hiatus for the extension of the sacculations. Illustrating again the inconstancy of the bronchial changes is case V in which the bronchi in some instances present a mucosal infolding and partial stenosis suggestive of the anaphylactic guinea pig, while others are widely dilated with extensive sacculations—both of these occurring in a supposedly 'bacterial' type of asthma. Only in case IV (allergic?) is narrowing and stenosis of the bronchi at all generalized, although in two of the other cases, V ('bacterial'), and VII (doubtful etiology), the bronchi are much narrowed in some areas. In these three cases the bronchial stenosis has evidently been accomplished by infoldings and muscular spasm with exudate in the lumina playing a lesser part. In other cases the occlusion of the lumina is accomplished by the exudative products of the hyperplastic, bronchial mucous glands and mucosa (Curschmann's spirals, cellular débris). In practically all instances the smaller bronchioles are uniformly dilated, obviously the result of increased intrabronchial tension, which is in all probability also the cause of the bronchial sacculations. Of all the foregoing

changes it should be remarked that their variation in distribution is such that many fields have to be examined before one can come to definite conclusions regarding the type of pathologic change predominant.

The study of the cardiac changes becomes of interest in the light of the claim made by Alexander *et al*,¹⁸ that the heart remains remarkably free from damage in long continued bronchial asthma. They established the criteria of bronchial asthma in 50 patients with a ten year average duration of the disease and found only four with any clinical evidence of cardiac impairment that could be attributed to the asthmatic condition. They suggested that the increased intrathoracic pressure impedes the return of venous blood to the heart, thus leaving less work for the heart to accomplish during an attack. This is not borne out by the almost constant ventricular hypertrophy in this series at autopsy. Including a 13-year-old girl, and without note of sex or build, the average thickness of the left ventricular wall in all eight cases was 18.25 mm, and of the right ventricular wall 7.87 mm. The case of longest duration (VIII) presented a distinct right-sided preponderance with a right ventricular wall of 11 mm thickness. In spite of the fact that in each case the right ventricular wall is at least slightly increased in thickness, in only one (IV) is there any definite increase in subepicardial fat, while in two (III and VI) it is entirely muscular. Valvular lesions were lacking. The chief changes are atrophy, myocardial fatty infiltration, and patchy myocardial fibrosis.

Recent writings have referred to the

absence of associated tuberculosis,^{15, 20} often mentioned by the older writers. Only three of our cases showed tuberculous lesions and these consisted of old healed tubercles in the bronchial nodes, and in the liver in one instance.

Etiology

Until the conception of allergy became applicable to asthma, all investigators directed their attention to the determination of the inciting factors producing the periodic, dramatic crises with which they were called upon to cope. It was Ehrlich's pupil, Otto, who published in 1906 the first systematic investigations and conclusions regarding anaphylaxis. Four years later Meltzer¹⁸ suggested that asthma was an anaphylactic phenomenon, and that all asthmatics were sensitized to a specific substance. Forthwith a multitude of inciting factors were taken as proven, and the vial and needle of the immunologist became the chief weapons of the clinician against asthma. With von Pirquet's conception of human allergy, as contrasted to experimental anaphylaxis, certain factors were found necessary to establish the proof of a substance acting as an allergen, viz (1) An exact anamnesis, (2) a positive cutaneous reaction, (3) the passive transference of the cutaneous reaction to a healthy person by the serum of the allergic patient (Prausnitz-Küstner reaction), (4) the proof of the existence of the allergen in the individual's environment, (5) reproduction at will of the allergic phenomena by exposure of the unprotected patient to the allergen, by inhalation, ingestion or injection; (6) disappearance of the symptoms by removal of the offending allergen. It

soon became evident that only a small percentage of the cases studied were truly allergic, and for the susceptibility of the allergic individual, Coca²⁸ invoked the existence of an unknown immune body—the atopic reagent.

A variety of conditions thus became known as allergic manifestations—serum disease, hay fever, urticaria, certain types of enteritis and eczema, migraine, as well as bronchial asthma. In spite of the cases of asthma in which all the above postulates have been fulfilled, and many with apparent cure by reinjection of the specific allergen in desensitizing doses, there remain many cases in which none of the multitude of known allergens can be shown to be causative. And there are other findings which would indicate that there are more important, basic and underlying factors of which allergy is but an expression. Although only ten per cent of individuals are allergic in the ordinary sense of the term, Bloch and Karrer²⁰ demonstrated that practically any subject could be forced to allergic reaction, many bronchial asthmatics exist constantly in an environment laden with the specific allergen to which they are sensitive, and yet react only at irregular periods, many others, contrariwise, after removal to surroundings supposedly free from the causative factor do not necessarily improve and may even become worse; and finally, the proof is now overwhelming that the allergic substance, whatever it may be, is not necessarily protein in nature. Proof of this is found in the production by a non-protein extract of ragweed, of allergic phenomena exactly duplicating those ordinarily seen in cases sensitive to this plant.

An illustration of the latter, also, is the large group of cases showing susceptibility to chemical agents. Chief among this group are the coal tar derivatives—salicylic acid and its various derivatives and modification, antipyrin, methyl salicylate, benzoic acid and sodium acetate. Case I of this series, in spite of a 'bacterial' type of asthma, showed a definite susceptibility to, and severe paroxysms following, the administration of acetylsalicylic acid, death occurring in a seizure so induced. Van Leeuwen¹⁹ reports a similar case of susceptibility to acetylsalicylic acid manifested by severe asthma suddenly developing in a woman who had taken the drug for years previously, and also cites the case of another asthmatic who was susceptible to antipyrin. He concludes that such hypersensitiveness is acquired through absorption from the gastrointestinal tract, with altered reaction to the molecule as it is in the blood stream. In the case of sudden death reported by Wright,⁶ the asthmatic seizure commenced a short time after the administration of acetylsalicylic acid and codeine. Like van Leeuwen's case, adrenalin was ineffective. By no stretch of imagination can such results be interpreted as due to the actual toxicity of aspirin. This has been determined by de Jankovich,²¹ who reported six cases of fatal poisoning with the only notable autopsy finding that of multiple hemorrhages, and fixed the lethal dose at 20 gms.

It is therefore evident that even as the atopic reagent in the hypersensitive individual is unknown, so is the specificity of the allergic antigen a matter of doubt. The basic laws of immunology demand that to establish the iden-

tity of a specific allergic reaction, the experimental repetition of passive sensitization with an antibody-containing serum must be proven. The inability to obtain such a reaction with many supposed allergic antigens makes it impossible to apply the general principles of so-called protein anaphylaxis to other forms of hypersensitiveness.

For this reason it seems impossible to accept as proven the conception of bacterial protein acting as a basic, allergic, etiologic factor to produce a clinical entity known as 'bacterial asthma'. Introduced by Walker²² in 1917, the term was immediately adopted by clinicians as a most opportune label for those asthmatics who did not react to any known allergen, and in whom one could demonstrate the presence of focal infection, preferably in the accessory nasal sinuses, or existing as a chronic form of bronchitis. As early as 1922, Cooke,²³ in a critical review of Walker's work showed that the latter had demonstrated clinical improvement under nonspecific bacterial vaccine treatment, regardless of the reaction obtained with the bacterial protein used. Walker's results showed no conformity with local cutaneous reactions or recovery of specific organisms in the vaccines. Many of his best results were obtained with *Staphylococcus aureus* vaccine, although that organism had not been recovered. Cooke, in 50 cases of bronchial asthma, found only two which reacted to any type of organism with an immediate urticarial wheal, and even in these the bacteria to which they thus appeared sensitive could not be recovered from the sputum or nasal cultures. He was quite unable to elicit any constitutional re-

actions by the use of bacterial preparations as allergens, and concluded that they do not act as fundamental allergens *per se*, that the cutaneous test with bacterial preparations was useless, and that the conception of bacterial asthma was based entirely on analogy Six year later, Zinsser²⁴ supported these conclusions and confessed to knowing of only one case where eradication of a sinus infection associated with bronchial asthma gave relief Unger,²⁵ reporting 189 patients with bronchial asthma and hay fever treated by sensitization tests and injections in the clinic at Northwestern Medical School, is silent regarding any results with bacterial reactions or vaccines It is a fact worthy of note that the cases in this series who received treatment with supposed specific vaccines uniformly became much worse, one case, during such treatment passing into a prolonged series of seizures that eventually resulted in death (case V)

The case against the specificity of bacterial allergens becomes even more

convincing through the lack of any uniform pathological changes in the asthmatic so classed in spite of effort to establish such an entity In a recent publication, Steinberg and Figley,⁵ on the basis of autopsy findings in two cases attempted to differentiate the pathologic changes in 'non-bacterial allergic' and 'bacterial' asthma, referring particularly to the contrasts in emphysema, atelectasis, bronchial exudate, muscular hypertrophy, destruction of epithelium, and eosinophilia in the two types Tables I and II show how variable the changes are in both types This has been discussed already in regard to the eosinophilia, the epithelial destruction is more likely an evidence of activity of the process, while the other changes seem to vary in individual response, irrespective of etiology

It is evident at least that in spite of the apparently well defined relation of the disease to allergy in a few cases, in the majority of instances we are without definite knowledge as to the underlying factors of asthmatic etiology. As

TABLE I
Evidences of the Thymicolymphatic Constitution

	THYMUS	LYMPHOID SYSTEM	ADRENALS	AORTA
CASE I	Persistent and hyperplastic	Hyperplastic	Hypoplastic	Hypoplastic
CASE II	Slightly persistent and hyperplastic	Sinus catarrh	Moderately hypoplastic in both cortex and medulla	Moderately hypoplastic
CASE III	Persistent	Hyperplastic	Hypoplastic	Hypoplastic
CASE IV	Persistent	Slightly hyperplastic	Markedly hypoplastic	Hypoplastic
CASE V	Persistent	Markedly hyperplastic	Hypoplastic	Markedly hypoplastic
CASE VI	Persistent and hyperplastic	Hyperplastic	Hypoplastic	Hypoplastic
CASE VII	Very marked and persistent hyperplasia	Markedly hyperplastic	Hypoplastic	Markedly hypoplastic
CASE VIII	Persistent and hyperplastic	Hyperplastic	Moderately hypoplastic	Moderately hypoplastic

TABLE II
Bronchial Pathology

CASE NO	DURATION OF DISEASE	LUMINA	EPITHELIUM	BASALMENT MEMBRANE	SUBMUCOSAL LAYER	MUSCLE	MUCOUS GLANDS	BRONCHIAL NODES
I	5 years	Dilated Some occluded Curschmann's spirals	Not remarkable	Thick and hyaline	Eosinophilia	Moderately hypertrophic	Prominent	
II	8 years	Dilated Some occluded Curschmann's spirals	Not remarkable	Thick and hyaline	Eosinophilia	Hypertrophic	Prominent	
III	8 months	Dilated Some occluded Curschmann's spirals	Not remarkable	Thick and hyaline	Eosinophilia	Slightly hypertrophic	Prominent	Marked eosinophilic infiltration
IV	2 years	Narrow Slight cellular exudate	Not remarkable	Thick and hyaline	Thickened Cellular Eosinophilia slight	Markedly hypertrophic	Not Prominent	
V	14 years	Marked variation Mucinous exudate	Small ulcers	Very thick and hyaline	Eosinophilia	Irregularly hypertrophic	Hypertrophic	
VI	10 years (approx)	Mucoid exudate	Not remarkable	Thick and hyaline	Eosinophilia	Hypertrophic	Hyperplastic	Eosinophilic infiltration
VII	3 years	Variable Mucinous exudate	Not remarkable	Very thick and hyaline	No eosinophilia	Uniformly hypertrophic	Hyperplastic	
VIII	45 years	Universal dilatation Extensive sacculations	Marked hypertrophy	Very thick and hyaline	Thickened No eosinophilia	Hypertrophic	Not Prominent	

to the actual inciting factor of the individual paroxysm, we are no nearer the truth than were the disciples of the school of Salerno, nor are we able to describe the dramatic phenomena in such graphic phrases as did Floyer in 1698. In general one can say that the symptoms are equivalent to an expression of hyperstimulation of the parasympathetic nervous system. Hansen,²⁶ in addressing the Royal Society of Medicine in 1929, correlated this fact with the conception of the psychophysical coordination of the individual by which the autonomic and vegetative nervous systems function in harmonious interrelation. Thus, by the reaction of the higher centers upon the more lowly neurogenic system, can one perceive some reason for the well established cases of asthma constantly exposed to the inciting allergen, but in whom the asthmatic paroxysm occurs generally after periods of mental stress.

Even with this rather vague hypothesis as a reason for onset in some cases, even with the possibility of van Leeuwen's late theory of 'colloid substances of unknown composition in the atmosphere', one is driven to seek a deeper anatomic substrate upon which these inciting factors act. In such a search, first of all, one is confronted by the frequent repetition of a familial history. The heredity of the allergic soil is a well known and established fact. In addition, the asthmatic, as Davidson²⁷ points out, often gives a family history not only of asthma, hay fever, urticaria and other definite allergic phenomena, but also nervous manifestations such as migraine, epilepsy, hysteria and other neuroses. The majority of cases of true asthma occur in middle

aged people who show prematurely a degenerative reaction to the stress and strain of living, often with accompanying chronic bacterial infection, focal or otherwise. Such lowering of vital force is evidenced in several of the cases in this series by repeated and prolonged infections which in themselves would have been but transitory with the normal individual.

Seeking more definite anatomic and histologic evidence of deviation from the accepted normal, each case in this series shows conclusive evidence of a pathologic constitution. Table III shows the evidence of such in the lymphoid and chromaffinic tissues and in the vascular system. The thymicolymphatic constitution, persistent in later life, provides that receptive anatomic substrate in which the so-called allergic antigen is best able to elicit those diverse phenomena known as allergic reactions. It is reasonable to suppose that our designation 'allergen' may be applied in most instances to any substance which possesses the ability of acting upon this pathologic constitution in such a manner as to provoke an expression of its altered state. More specifically, the allergic state is an altered reaction, but it is the altered reaction of this inheritable, hypoplastic type of constitution often associated with an exudative diathesis, and upon which a multitude of exogenous, provocative factors, ordinarily without influence on a normal soil, are capable of producing the expressions of the diseased state. Such an individual may reach middle life before showing definite pathologic evidence of his constitution, and then, as in case III, under some added load as an acute infection,

TABLE III
Presumable Etiology and Cardiac Condition

CASE NO	AGE	ETIOLOGY	TERMINAL CONDITION	LEFT VENTRICULAR WALL,	RIGHT VENTRICULAR WALL,	OTHER CARDIAC CHANGES
I	43	Bacterial	Asthmatic paroxysms	20 mm	8 mm	Patchy myocardial fibrosis Endocardial sclerosis
II	75	Allergic	Asthmatic seizures, lobular pneumonia	25 mm	6 mm	Myocardial atrophy, fibrosis Endocardial sclerosis
III	53	Bacterial	Asthmatic seizures	22 mm	10 mm	Fatty changes Hypoplastic myocardium
IV	58	Allergic (?)	Asthmatic paroxysms	17 mm	6 mm	Fatty changes Atrophic myocardium
V	36	Bacterial	Asthmatic paroxysms	20 mm	6 mm.	Fatty changes
VI	13	Both (?)	Lipiodol reaction	13 mm	7 mm	Myocardial atrophy and Zenker's necrosis
VII	56	Both (?)	Lobar pneumonia	15 mm	7 mm	Endocardial sclerosis
VIII	58	Allergic	Sarcoma of uterus pneumonia	17 mm	11 mm	Fatty change Endocardial sclerosis

inhalation of chemical fumes, or mental stress, may suddenly exhibit a profoundly altered reaction which may be so constantly severe and depressive as to bring about dissolution in a comparatively short time.

SUMMARY

1 Eight cases of bronchial asthma with autopsy findings and microscopic studies are reported. In five of these death resulted during asthmatic paroxysms.

2 The chief local pathologic changes are—

- a Invariable thickening and hyaline change of the basement membrane of the bronchi
- b Eosinophilia.
- c Varying degrees of muscular hypertrophy and glandular hyperplasia dependent upon

the individual reaction to vagal (?) stimulation

- d Bronchial sacculations occurring through the mouths of the mucous glands.
- e. Epithelial changes such as hypertrophy and metaplasia, interpreted as evidence of chronicity.

3. Review of clinical, immunological and pathologic evidence fails to support the conception of such an entity as bacterial bronchial asthma.

4 Each of the cases of this series is proven to be of a thymicolymphatic constitution. It is suggested that bronchial asthma and many other 'allergic' phenomena are but the expression of the response of this inheritable constitution to exogenous substances—'allergens'

REFERENCES

- ¹GRIMM, V. Das Asthma, 1925, Gustav Fischer, Jena
- ²RACKEMANN, F. M. Fatal asthma; report of a case with autopsy, Boston Med Surg Jr, 1926, cxciv, 531-534.
- ³KOUNTZ, W. B., and ALEXANDER, H. L. Death from bronchial asthma, report of three cases, Arch Path, 1928, v, 1003-1019
- ⁴DEHNTR, W. Beitrag zur Pathologie des Asthma bronchiale, Klin Wchnschr, 1927, vi, 1412-1417
- ⁵STEINBERG, B., and FIGLEY, K. D. Pathology of asthma, non-bacterial allergic and bacterial types based on autopsy material, Jr Lab and Clin Med, 1928, xiii, 921-942
- ⁶WRIGHT, C. B. Death from bronchial asthma, Jr Am Med Assoc, 1930, xciv, 1218-1221
- ⁷HUBER, H. L., and KOFSSLER, K. K. Pathology of asthma, Arch Int Med, 1922, xxx, 689-760
- ⁸MÖCKELTGERG, J. G. Zur pathologischen Anatomie des Bronchialasthmas, Verhandl d deutsch path Gesellsch, 1909, xiii, 173-180
- ⁹BERKART, J. I. B. On bronchial asthma, its pathology and treatment, 1889, J. and A. Churchill, London
- ¹⁰EINTHOVEN. Über die Wirkung der Bronchialmuskeln, nach einer neuen Methode untersucht, und über Asthma nervosum, Arch f d ges Physiol, 1891-1892, li, 367-445
- ¹¹DIXON, W. E., and BRODIE, T. G. Contributions to the physiology of the lungs. Part I. The bronchial muscles, their innervation and the action of drugs upon them, Jr Physiol, 1903, xxix, 7-173
- ¹²AUER, J., and LEWIS, P. A. A demonstration of the cause of acute anaphylactic death in guinea pigs, Proc Soc Exper Biol and Med, 1910, vii, 29-30.
- ¹³MILTZER, S. J. Bronchial asthma as a phenomenon of anaphylaxis, Jr Am Med Assoc, 1910, lv, 1021-1024

- ¹⁴FASCHINGBAUER, H Beitrag zur Pathogenese und Anatomie des Asthma bronchiale, Wien Arch f inn Med, 1922, iv, 349-378
- ¹⁵UNVERRICHT Pathologie und Therapie des Asthmas, Ztschr f arztli Fortbild, 1928, xxv, 315-319
- ¹⁶ALEXANDER, H Bronchial asthma, its diagnosis and treatment, 1928, Lea and Febiger, Philadelphia
- ¹⁷BOUGHTON, T H Anaphylactic death in asthmatics, Jr Am Med Assoc, 1919, lxxiii, 1912-1914
- ¹⁸ALEXANDER, H L, LUTEN, D, and KOUNTZ, W B Effects on heart of long-standing bronchial asthma, Jr Am Med Assoc, 1927, lxxxviii, 882-884
- ¹⁹VAN LEEUWEN, W S Pathognomonische Bedeutung der Überempfindlichkeit gegen Aspirin bei Asthmatikern, Munch med Wchnschr, 1928, lxxv, 1588-1590
- ²⁰BLOCH, B, and KARRER, P Chemische und biologische Untersuchungen über die Primelidiosynkrasie, Vrtljsschr. Naturforsch Ges Zurich, 1927, lxxii, Beibl 13
- ²¹DE JANKOVICH, L Les empoisonnements morbides par l'aspirine, Ann de méd lég, 1928, viii, 7-10
- ²²WALKER, I C, and ADKINSON, J Studies on *Staphylococcus pyogenes aureus*, *albus* and *citreus*, and on *Micrococcus tetragenus* and *Micrococcus catarrhals*, Jr Med Research, 1916-17, xxxv, 373-390
- ²³COOKE, R A Studies in specific hypersensitiveness, new etiologic factors in bronchial asthma, Jr Immunol, 1922, vii, 147-162
- ²⁴ZINSSER, H Significance of bacterial allergy in infectious diseases, Bull New York Acad Med, 1928, iv, 351-383
- ²⁵UNCER, L Clinical investigations in allergy, review of 189 patients of asthma and hay fever clinic, Jr Lab and Clin Med, 1927, xii, 1159-1163
- ²⁶HANSEN, K Allergic and psychical factors in asthma, Proc Roy Soc Med, 1929, xxii, 789-800
- ²⁷DAVIDSON, M Asthma, Med Press 1928, cxxvi, 363-366
- ²⁸COCA, A F Relation of atopic hypersensitiveness (hay fever, asthma) to anaphylaxis, review of recent literature, Arch Path and Lab Med, 1926, i, 96-118

Chronic Appendicitis*

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MORE half hours may be spent puzzling over whether to operate for chronic appendicitis or not than over any other major surgical condition. By the time a patient with gallbladder disease consents to operation, the symptoms are usually definite, and in the great majority of cases there have been sharp colics. Those suffering from goiter usually wait until they are nervous and have lost weight before consulting a surgeon. Patients with cancer or with peptic ulcer usually have well defined clinical pictures by the time of operation. On the other hand, the public is so well informed and apprehensive of delay in appendicitis that patients usually seek operation immediately if appendicitis is diagnosed.

Discussion will be limited to chronic appendicitis—with pain, usually of long duration, either repeated or persistent, in the right lower quadrant, with no rise in temperature nor leukocytosis.

DIAGNOSIS

There is a voluminous literature, which I will not attempt to review. Each year brings forth its quota of critical analyses of cases, positive opinions or impressions, diatribes against appendectomy unless that organ be acutely inflamed, etc.; and if one

glances over several of these, or some of the reviews, he will be surprised at the wide differences of opinion still existing as to the indications for what is apparently one of the simplest operative procedures we do. On one side is Carnett¹ who states that "there is no such clinical entity as chronic appendicitis", and that pain in the right side is very frequently due to intercostal neuralgia, which can even simulate acute appendicitis. On the other side are several noted internists as Rehfuess and Boas, surgeons as Deaver, who, while picking their cases carefully and refusing to operate upon or have operated upon the majority of those complaining of right sided pain, nevertheless state positively that appendectomy does cure chronic pain in the right side, even chronic pain in the upper abdomen with right lower quadrant tenderness; and that sometimes the diagnosis is most difficult, being made only after right lower quadrant exploration, and then is not definite until one has followed the patient and he remains free from pain. Gaither,² in a careful review based upon 1,000 cases, concludes that "chronic appendicitis is at the present day a widespread and often unrecognized malady, it is often masked by the prominence of its secondary manifestations, it should be thought of in all cases of disordered digestion presenting motor and

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secretory symptoms, in every case of chronic constipation, in gastric upsets without definite ulcer symptoms, in intestinal dyspepsia and toxemic states"

Figures can easily be obtained showing that to operate, or not to operate, for chronic appendicitis is indeed a major problem

Lichty,³ analyzing 517 consecutive cases in which "the complaints after the operation were the same as before the operation", found that in 243, or almost one-half of them, appendectomy had been performed for chronic appendicitis. Andresen⁴ found that ten per cent of the total admissions to his gastro-intestinal clinic at the Long Island College Hospital had had an appendectomy, and that among similar cases in private practice there were 13 per cent who had had appendectomy. Others have put this figure as high as 25 per cent.

There is no doubt but that many appendectomies are part of a long chain of useless and now discarded operations. These started with ovariectomy, then included operations for retrodisplaced uterus, chronic salpingitis, adhesions, various uplifts for neuralgia, as movable kidney, ptotic stomach and bowel, chronic cholecystitis, finally reaching the appendix. Indeed, these procedures have in the past all been done for this same chronic abdominal pain, generally right sided. But there is also no doubt that most of these procedures, judiciously employed for chronic complaints, produce striking and grateful cures.

During the past five to ten years, several surgical clinics have carefully analyzed their results following appendectomy, with the realization that

though there are still considerable differences of opinion, certain types are more clearly seen as potential poor results, and operation avoided. Poor results with persistence of symptoms, range from 10 to 70 per cent, frequently quoted as 30 to 40 per cent. There are several analyses, in which three to four years after 30 to 40 per cent of failures were reported following appendectomy, 10 per cent of failures are now reported.

There is rather general agreement that two types of chronic appendicitis can be differentiated.

1 Repeated painful attacks, usually starting with an acute attack. There are only one or two dissenters from the opinion that such patients should have appendectomy, and that this generally brings relief. Several state that if appendectomy were limited to cases in which repeated attacks with intervening free intervals were described, the operation, patient and surgeon would be much better off. "It is a wise rule never to diagnose chronic appendicitis and never to operate upon such a case without a history, definite or perhaps even indefinite, localized or with referred symptoms, which may be regarded as a probable attack of acute or subacute appendicitis", says Thomas R. Brown.⁵ This viewpoint is rapidly gaining adherents.

Rolleston, Aschoff, Alvarez, and Seale Harris, have all stated that all chronic appendicitis cases have had previous attacks. Lichty³ makes no diagnosis of appendicitis unless there have been characteristic acute attacks.

2 There is a second group, described alike by no two writers, in which most of the difficulty and confusion lie. This is made up of cases

of persistent right-sided pain with reflex gastro-intestinal symptoms of various forms

Crohn⁶ has described these cases under four groupings:

I Young adult men, in whom the distress simulates gastric or duodenal ulcer, probably due to pylorospasm. There is not the periodicity usually associated with ulcer, in these cases the distress is more irregular and intermittent, it comes long after meals, two to three hours, is usually located just above the umbilicus, and there are long free intervals

II Patients who have had obstinate constipation for years, with mild reflex gastric symptoms — heartburn, pyrosis soon after eating, halitosis, bad taste in the mouth, poor appetite. Sometimes there is no abdominal pain. Occasionally a case of this type will develop a sudden severe gangrenous appendicitis

III Indefinite and continuous low abdominal pain in the right lower quadrant, sometimes in the right hypochondrium. These cases simulate gallbladder disease, or occasionally new growth. When heartburn, belching and poor appetite occur in the neurotic, there is a natural tendency to make light of these symptoms

IV Unusual cases presenting chiefly diarrhea with no gastric symptoms. There may be severe upper abdominal cramps with nausea and vomiting, and no right lower quadrant tenderness

There is a good deal of difference as to operative indication in this group. Deaver insists that pylorospasm with distressing dyspepsia may be of appendiceal origin even if there is no right lower quadrant tenderness, and will be cured by appendectomy. Boas and Rehfuess, also, sometimes advise appendectomy for chronic abdominal complaints as a diagnostic procedure. If the symptoms are relieved, the diagnosis is correct. Most other recent writers dissent from this viewpoint,

and urge extreme caution in cases with no recurrent attacks

FAILURES

Perhaps most can be learned from analyses of failures. Several of these, from very careful follow-up services, have been reported recently

Whipple⁷ analyzed 53 failures making the following final diagnoses in these cases

Neuroses of various types	21
Visceroptosis	8
Colonic stasis—spastic	
descending colon	3
Tender cecum bound to adnexa	2
Tuberculous lymphadenitis	} 1 or 2 each
Cholecystitis	
Gastric ulcer	
Duodenal ulcer	
Sacro-iliac sprain	
Chronic colitis	
Pulmonary tuberculosis	

He cautioned against operating upon (a) those asthenic ptotic individuals belonging to the so-called carnivorous type with a long standing history of pain and tenderness in the right lower quadrant, and (b) those having many and exaggerated complaints, among them pain and tenderness in the right lower quadrant. These patients have neuroses of one kind or another and may be either the well nourished or the ptotic type

A similar list of 230 diagnoses in private patients who had had appendectomy without relief is given by Andresen⁴

Gastroduodenal ulcer	36 per cent
Gastritis and duodenitis	26 per cent
Gallbladder disease	35 per cent
Colitis	21 per cent
Pancreatitis	0.4 per cent
Adhesions	25 per cent
Hernia	7 per cent
Hemorrhoids	7.5 per cent
Carcinoma	3 per cent
Food allergy	7 per cent

Gibson's⁸ conclusions are frequently quoted and bear repetition. To avoid disappointment he advises

- 1 Comprehensive and detailed history taking
- 2 Careful physical examination
- 3 Excessive care before advising operation in women and all more mature individuals
- 4 Careful search at time of operation for other lesions
- 5 The sedulous avoidance of operations upon neurasthenics
- 6 Restrained, if there are no definite attacks or localized pain with nausea or vomiting
- 7 A good sized incision and a thorough exploration

Another study of end results, where 26 per cent of unsatisfactory results are recorded, ends as follows⁹

"The following points should be seriously considered in making a definite diagnosis of chronic appendicitis with a promise of permanent relief by operation

1 A complete detailed history of frank attacks. The nearer the history approaches the cardinal signs of appendicitis the better the prognosis for cure

2 Physical examination should be most thorough, ruling out especially genito-urinary and gynecological conditions and not overlooking lung pathology

3 Asthenic individuals, both male and female, with a suggestive neurotic make up should be subjected to long periods of observation with all refinements of diagnosis

4 Large incision

5 The finding of a diseased appendix is not enough to guarantee the patient complete relief

6 Delivering the appendix through a small incision and the use of dry sponges may favor the formation of adhesions"

Note the similarity in the conclusions arrived at in these two studies

Some of the facts brought out by these postoperative analyses of failures—and they all agree in substance—

are. Beware if there are no acute attacks. There are more failures in women than in men. There are more appendectomies performed for chronic appendicitis in women than in men, and the ratio should be more nearly the ratio of appendectomy for acute appendicitis in women and men respectively. Everyone who has analyzed his results urges one to beware of the neurasthenic, the neurotic, the long, thin viscerotropic persons of both sexes. They had best be left alone, or operated upon after very careful observation and exclusion of all other possible causes of abdominal pain and discomfort. One hospital reduced its failures from ten per cent to one per cent by first referring suspected chronic appendicitis cases to a psychiatrist.

DISCUSSION

From the above analyses, plus my own experience, the following generalizations can be made

Needless to say, chronic appendicitis should always be an exclusion diagnosis. Certain types and age groups are more apt to have chronic appendicitis. All analyses have shown that complicating conditions—ulcer, gallbladder disease, ureteral and kidney conditions, etc—are more frequent the older the patient. In children, the attacks may be milder, and are more frequently overlooked. The tenderness and pain may be located higher, at the level of the umbilicus, because the cecum frequently lies higher. There is not the confusion of diagnosis which ulcer, gallbladder disease, salpingitis, etc., bring in later life, but there is more apt to be abdominal pain referred from pulmonary or upper respiratory infection than in adults. In-

cidentally, the incidence of acute appendicitis is higher in epidemics of upper respiratory infections than at other times. Personally, I am more apt to believe a child when he complains of transient, but repeated bellyache than an adult, and think these cases usually are appendicitis. If in doubt I tell the mother that the child probably has appendicitis, should be watched carefully, and taken care of at the first recurrence of trouble. I have removed some surprisingly involved appendices in children after mild attacks, and do not recall as many postoperative failures as in adults. A normal child should not know he has a "stomach", and repeated unexplained "bellyaches" can be considered more significant in children than in adults.

URETERAL CALCULUS

Ureteral calculus is not hard to avoid if one is on guard. None of the postoperative analyses record more than two or three cases which subsequently proved to be urinary calculi. A calculus in a young adult usually gives a severely painful seizure, with the pain out of all proportion to the local findings. The cases I have had the most difficulty with have been between 35 and 50 years of age, generally heavy set men, with a dull right-sided ache. A few white blood cells may be all the urinary findings given by a large kidney stone. When there is the slightest doubt, I look at the sediment myself.

GALLBLADDER DISEASE

The gallbladder is coming to the fore as the chief rival of the appendix. Disease of this organ is now one of the most frequent affections for which

laparotomy is undertaken. It is being diagnosed earlier in life than formerly, and since the Graham-Cole test (which has a high degree of accuracy), is being found more frequently.

Graham believed that the majority of cases in which symptoms were thought to be due to chronic appendicitis are due to gallbladder disease and spastic constipation. Indeed, Jordan and Lahey¹⁰ recommended that if certain abdominal symptoms — gas, distress, and more or less atypical pain — do not respond to rest in bed, bland diet, etc., cholecystectomy is sometimes indicated, even if the gall bladder fills well with the dye. I have had one such case in a heavy set man, whom appendectomy failed to relieve of mild but persistent dyspepsia. The gallbladder filled well, was grossly normal on removal, but microscopically showed chronic inflammation of moderate degree. The patient has remained free of abdominal distress he had had for years. Irland¹¹ goes one step further and feels that the gallbladder may be frequently responsible for symptoms which in no way implicate the digestive tract, the gallbladder acting as a silent focus of infection.

This important rôle of the gallbladder has been stressed only for the past few years. Perhaps some of the poor results in patients classed as neurasthenics have this explanation.

SPASTIC CONSTIPATION AND ALLERGY

Students of diseases of the colon feel that this organ is more frequently deranged than is the stomach "although the stomach has had more advertising". Its most common malfunction is a condition of localized spasm, caused by undue muscular tonus which, in turn,

probably results from abnormal nervous stimuli—imbalance of the sympathetic nervous plexuses governing the colon. Duke, Vaughan, Rowe¹² and others feel that these manifestations are allergic in nature and due to food sensitization. Cramps and flatulence are produced, and similar heightened neurogenic secretory stimuli produce mucous diarrhea. These localized spasms can occur throughout its extent, but are more common in the descending colon. When prolonged, intestinal stasis is produced proximalward, which may easily result in secondary dilatation and tenderness in the cecum, the rolling, gas-filled cecum which was thought significant of chronic appendicitis. Kantor¹³ feels that the position of the cecum is important clinically. If it is high-lying, there are few symptoms. If low-lying, symptoms are common, the drag of the colon on adjacent organs (possibly the duodenum) perhaps being responsible.

Eggleston¹⁴ reported that 22 per cent of 100 spastic colon cases had had appendectomy without relief. These individuals, preponderantly women, long, thin, viscerotropic, with cold extremities, low blood pressure, easily fatigued, "belly conscious", are avoided by all who know. Their dyspepsia, flatulence, cramps, and diarrhea are expressions of motor and secretory dysfunction of the colon due either to sympathetic nervous system imbalance, or perhaps localized allergic spasm and edema, and are not to be explained upon an anatomical basis such as appendectomy might cure.

Another pitfall which has been recognized recently is abdominal allergy—abdominal pains due to food sensitivity. Osler¹⁵ wrote an article in

1904, "On the surgical importance of visceral crises in the erythema group of skin diseases", cautioning against the danger of unnecessary surgery. Since then, the old fashioned angio-neurotic edema, or urticaria, modernly conceived as the characteristic lesion of allergy, is made to explain a host of apparently unrelated phenomena. Muscular spasm and mucosal congestion and edema, the pathological changes in allergy, can occur anywhere in the body. In the brain, they are said to produce cerebral edema for which decompressions or fifth nerve injections have been done. In the alimentary canal, canker sores, coated tongue, ulcer-like pains, gastro-intestinal bleeding, pruritus and have all been ascribed to local sensitization of various parts of the alimentary mucous membrane.¹² The liver cells and gallbladder mucosa becoming edematous, cause right hypochondriac pain for which gallbladders have been removed. Urinary symptoms (dysuria, frequency, etc.), some forms of hypertension, hypotension, disturbed menstruation, are all described as due to sensitization to certain foods or other articles. A localized spasm of the Fallopian tube has been reported as simulating ectopic pregnancy, the sting of *Pediculus pubis*, or of the bed bug is presumably due to a localized allergy from the toxins excreted.

Seriously, however, food allergy may cause various atypical abdominal symptoms, pains, colics, distress, distention, nausea, pyrosis, vomiting, spastic constipation, diarrhea and colitis. The pains are more often generalized and in the lower abdomen. Appendectomy has been performed frequently when the pains could have

been cured by elimination of certain foods, generally wheat, milk or eggs. More important still, distress continues until the offending factor is sought out and eliminated

The following case history demonstrates the confusing picture which abdominal allergic manifestations may present.

S M was a boy, aged 13 years. On his first visit to the clinic in June, 1929, it was noted that he had had two attacks of pain in the right lower quadrant, each of two weeks' duration. During the attacks, pain came two or three times daily, with no relation to food. Flexing the right thigh and lying down stopped the pain. There was slight tenderness over McBurney's point, and the x-ray diagnosis was disease of the appendix.

He returned on April 12, 1930, having recently had another attack, this time with the pain confined chiefly to the epigastrium. Because of marked dermographia he was referred to the allergy clinic (Dr Geo L. Waldbott) for study. It was found that he had had eczema; his father and one sister also had had eczema. There was no other positive finding except an eosinophilia of seven per cent. He was sensitive to cheese, wheat, beef, asparagus, rabbit hair, eggs, and chicken feathers. Under treatment by means of elimination of these articles aided by injection of their extracts the child did very well until the ragweed season started, when there was vomiting, abdominal pains, upper respiratory catarrh and exacerbation of the eczema. On one occasion, injections of ragweed produced severe pain in the abdomen. There has been occasional slight recurrence of pains and sensitiveness, but the boy had gained 15 pounds and was much improved when last seen in March, 1931.

One must be careful here. I have seen attacks recur after the patient was supposedly cured by treatment directed against food allergy, necessitating appendectomy.

OTHER CONDITIONS

It is well to remember also that sacro-iliac disease causes anterior abdom-

inal tenderness. (Baci's point). A three-eighths inch lift on the right heel has corrected a lumbar lordosis for which three operations on the abdomen had been done. Tuberculosis and cancer of the cecum are frequently indistinguishable from chronic appendicitis.

As noted, many writers state that unless there is tenderness in the right lower quadrant no operation should be undertaken. I have had three patients in whom there was no right lower quadrant tenderness and in whom definite chronic appendicitis was found.

The rare or unusual case of appendicitis can simulate almost any intra-abdominal disease—depending chiefly upon its position. Ewald¹⁵ in 1899 introduced the term "appendicitis larvata" to describe cases where "the pain of which the patient complains, leads him and the doctor in the first instance to anything but an illness originating in connection with the appendix." Pain under the left costal margin, at the right costal margin (appendix lying underneath the liver), or behind the kidney, may be the only symptom of appendicitis. An appendix plastered in the pelvis, or wrapped about the sigmoid or rectum may give diarrhea, vomiting, loss of weight, mass, etc., exactly simulating carcinoma.¹⁶ Underneath all the coils of intestine, it may simulate mild subacute obstruction. Hematemesis and hematuria can be caused by chronic appendicitis.

X-RAY DIAGNOSIS

A battle royal has raged concerning the value of X-ray examination in chronic appendicitis. Filling, non-filling, segmentation, delayed emptying, tenderness over the appendix, etc., all have proponents and opponents. An

important practical consideration frequently concerns whether a patient of moderate means should be subjected to the (for him, considerable) expense of an X-ray examination. The late Dr. Carman of the Mayo Clinic was rather disdainful of the diagnostic value of the X-ray in appendicitis, and this was well known.

Deaver expressed himself rather forcefully¹⁷

"It is my experience that if a careful study of the history with painstaking physical examination does not make the diagnosis it will usually not be made by the roentgen ray study.

"Cholecystography and roentgen ray examination have not given me so much satisfaction in differentiating between the chronic gallbladder and the chronic appendix as have a carefully taken history and a carefully conducted physical examination."

One internist states that the main cause of needless appendectomies is the "furor operandi" of ambitious surgeons, whose chief aid and abettor is the roentgenologist. Rehfuess blamed the disinterested surgeon and said he never saw a surgeon fluoroscope a patient, and a surgeon was no more competent to pass upon X-ray evidence than a roentgenologist was to remove the appendix.

As with everything, there is a middle course. Lahey's opinion was "Expertly applied, wisely interpreted and properly correlated no one can question its (roentgenological examination of the appendix) inestimable value."¹⁸

Merritt and Moore¹⁹ very recently have stated that "by many, this subject (X-ray examination of the appendix) has been unheeded, and the method has failed, we believe, to receive the consideration that it merits."

The X-ray examination is sometimes more informative than other examinations, as in the following case.

Mrs. N. P., aged 42 years, was first seen August 11, 1930, complaining of "indigestion" and gas on the stomach. For several months she had had occasional spells of indigestion. During the past two months, she had had three attacks of more generalized abdominal pain, lasting two to three days, accompanied by watery diarrhea. The pain was more on the left than the right side of the abdomen. There was no constipation. She had been on ulcer regime for five weeks. She had been in the country during the summer and there was some question about the well water used, several people having had diarrhea.

Examination revealed a pale, frail, ptotic woman, negative except for some general soreness over the left side of the abdomen, none elsewhere. X-ray (Drs. Evans and Reynolds) showed a long pelvic appendix which was tender, and retained barium 72 hours even though the cecum was empty.

Because the clinical picture was not clear, she was observed further. After one or two more general abdominal pain attacks, she developed a typical attack with pain in the upper abdomen shortly followed by soreness and acute tenderness in the right lower quadrant.

Operation revealed a long appendix, the midportion dilated by two moderate sized concretions, the tip thickened and sclerotic. She has remained well since the operation.

A roentgen examination which shows a tender, fixed appendix, is very helpful diagnostically. Tenderness moving with shifting of the appendix, is also diagnostic. A persistent kink representing adhesions at that site, or adhesions about the terminal ileum means disease in a high proportion of cases. If abdominal palpation elsewhere causes pain over the appendix, or pressure over the visualized appendix causes pain in other parts of the abdomen, this is significant.

On the other hand, "beading", seg-

mentation of the lumen, and incompetency of the ileocecal valve, are found frequently in normal persons. Stasis and delayed emptying certainly are not of as much importance as originally considered. Moore and Merritt¹⁹ do not mention any of these as X-ray signs of appendicitis. Kantor,¹³ from extensive X-ray and clinical studies of these cases, found that cecal stasis was even more common after appendectomy for chronic appendicitis than before operation, (27 per cent unoperated, 29 per cent appendectomized individuals) and adds facetiously that if the appendix were not removed, "there would be more stasis in it after operation than before" *

Unquestionably the chief usefulness of the gastro-intestinal series in these cases lies in excluding ulcer, gallbladder disease, and diseases of the colon, not forgetting the diagnostic aid of the flat kidney plate, and the help that establishing the anatomical position of the appendix gives in certain cases. Ulcer and appendicitis sometimes exist together. Deaver speaks of this. I do not think the incidence is as high as some have stated, maybe five to ten per cent would be correct. As mentioned above, several who have written on the subject feel that there is no upper abdominal dyspepsia which is cured by appendectomy. However, if the X-ray shows an irritable stomach, without ulcer, and a tender appendix, that, I think, is confirmatory evidence of appendicitis. But, after this is said my experience corresponds to the trend of recent opinion, there is a gradual rebirth or renaissance of the idea that a half hour's questioning, perhaps re-

peated two to three times, plus careful abdominal palpation is more valuable to the patient than most of the expensive tests. The follow-up studies generally note this. In their conclusions as to how to avoid unsatisfactory results, there is little mention of X-ray examinations, but all stress careful pre-operative history and examination, and knowledge of which types to avoid.

OPERATION

A word about the operation. There is a general feeling that it is devoid of mortality and complications, but there is a recorded mortality of 1.5 to 2 per cent in very good hospitals. I have never used a McBurney incision. Gibson,⁸ after his first analysis of failures in 1920, gave up the McBurney and uses entirely a large rectus incision, for exploration. However, a wide operative exploration is not a panacea for right-sided abdominal pain. In 73 of 102 cases it did not avert an unsatisfactory result.

Concerning the appearance of the appendix at operation, there is no doubt but that partial or irregular or complete obliteration of the lumen indicates a chronic process and relief will follow operation. Fecaliths are plugs of intestinal contents which have become stagnant in the appendix lumen and become inspissated, encrusted with mucous, lime salts, etc. Their presence is presumptive assurance of a good result. The doubtful types are where one finds only slight congestion, a dulling of the normal lustre of the serosal surface, or coiling or slight kinking of the appendix—appearances which one frequently sees when operating for disease of other intra-abdominal organs,

*Personal communication

and which seem like rather meager pathological changes upon which to explain all the patient's symptoms and to be the *picce de resistance* of all the study, trouble, and expense the patient and doctor have gone through

There is controversy here. Some deny that these slight findings represent chronic appendicitis. The truth is that the border line between pathological and physiological change in the appendix probably has not been defined, and that, as stated above, the only proof in many cases is that, having followed these patients and found them free from pain after operation, they probably had appendicitis. In other words, the preoperative examination may be more accurate than the findings at operation.

END RESULTS

I have summarized 50 of my own personal records of patients upon whom appendectomies had been done for chronic appendicitis in whom I knew the end results, followed three to six months later. All acute appendicitis cases were excluded. All these cases had had long continued pains, had normal temperature and normal blood count. There were no fatalities, and no postoperative complications. Thirty-seven cases had had previous attacks of right lower quadrant pain, with approximate freedom from pain between attacks and no other symptoms. As near as I know all of these were relieved. I either have a note that the patient was well or free from symptoms three to six months later, or a note from the attending physician that such was the case.

Of the remaining 13, there were four cases where there had been epi-

gastric distress associated with right lower quadrant attacks. One of these cases had an X-ray diagnosis of prepyloric and duodenal ulcer. All of these patients are cured following appendectomy.

Another case developed heartburn shortly after appendectomy (definite appendicitis was found at operation). Her pains in the right side have ceased, but she still has occasional heartburn relieved by alkalis. Two cases had only epigastric pain—no right lower quadrant symptoms, but examination revealed tenderness there. They were cured. Two cases had persistent right lower quadrant pain with no definite acute attacks. They are relieved. Three cases are unrelieved. One may have a chronic cholecystitis, the other two probably belong to the irritable colon group.

In one case, I made a frank error. This patient was vomiting, had abdominal pain, and also complained of deafness in the right ear, which I told her she could have attended to later. This deafness and the vomiting were due to central nervous system lues affecting the internal ear mechanism. It cleared up after antiluetic therapy.

Thus 75 per cent of the group had repeated attacks of right lower quadrant pain only, and all were cured. In the remaining group several were relieved of epigastric distress by appendectomy, and there is an occasional operation for persistent right sided pain or persistent epigastric distress, with good results. All of the four failures are found among these more atypical cases.

The age group as a whole is young: 2 over 40, 6 between 30 and 40, 17 between 20 and 30, 15 between 10 and

20. There are apparently no examples of chronic appendicitis in this series under 10 years of age. Although chronic appendicitis does occur in young children, most children under 10 years have acute appendicitis or a recurring acute attack. Incidentally, during the period of this series, there was one case in which operation was advised against, and the patient subsequently was completely relieved by appendectomy done elsewhere, also two cases in which operation was refused and the patients have remained well.

The series is not large, perhaps all subsequent histories and later developments are not completely known and perhaps some patients might have gotten well without operation. However, the review of these cases leaves the reiterated impression. It is time well spent when chronic appendicitis is suspected to examine a patient two or three times for one-half hour each time before deciding to do an operation. In this examination, the interpretation of the clinical history is the most important single factor in avoiding poor results.

REFERENCES

- ¹CARNETT, JOHN B. Chronic pseudo-appendicitis due to intercostal neuralgia, *Am Jr Med Sci*, 1927, clxxiv, 579-599.
- ²GATHER, ERNEST. Chronic appendicitis, *South Med Jr*, 1921, xiv, 190-199.
- ³LICHTY, JOHN A. Chronic appendicitis, *Jr Am Med Assoc*, 1922, lxxix, 887-893.
- ⁴ANDRESEN, A. F. R. Medical aspects of chronic appendicitis, *Am Jr Surg*, 1928-29, v, 372-377.
- ⁵BROWN, THOMAS R. Colitis, catarrhal, mucous and ulcerative, *Int Clin*, 1927, iii, 24-45.
- ⁶CROHN, B. B. Affections of the stomach, 1927, Saunders, 427.
- ⁷WHIPPLE, A. O. Quoted by Carnett.
- ⁸GIBSON, CHAS. L. Results of operations for chronic appendicitis, *Am Jr Med Sci*, 1920, clx, 654-663, also 1924, clxviii, 807-812.
- ⁹DAVIS, W. T. End results in chronic appendicitis, *Bull Moses Taylor Hosp*, Scranton, Pa., 1927, 1, No 8, 1-8.
- ¹⁰LAHEY, F. H., and JORDAN, S. M. Management of biliary tract disease, *Am Jr Surg*, 1931, i, 1-5.
- ¹¹IRLAND, ROBERT D. Early phases of gall-bladder disease, *Jr Missouri State Med Assoc*, 1931, xxiii, 73-75.
- ¹²ROWE, ALBERT H. Food allergy, Lea and Febiger, 1931, p. 108-140.
- ¹³KANTOR, J. L., SCHLESER, S., and MARKS, J. A. Colon studies VI. Cecal stasis, *Am Jr Roent and Radium Therapy*, 1930, xxiv, 1-20.
- ¹⁴EGGLESTON, E. L. Colitis—spastic type, *Jr Am Med Assoc*, 1928, xci, 2049-2053.
- ¹⁵OSLER, WM. Surgical importance of visceral crises in the erythema group of skin diseases, *Am Jr Med Sci*, 1904, cxxvii, 751-754.
- ¹⁶DZIALOSZYNSKI, A. Appendicitis chronica unter dem Bilde eines Rektumkarzinoms. *Centralbl f Chir*, 1928, lv, 2568-2570. Abst in *Pract Med Series Handbook Gen'l Surg*, 1929, 461.
- ¹⁷DEAVER, JOHN B. Chronic appendicitis, *Am Jr Med Sci*, 1929, clxxvii, 749-758.
- ¹⁸CHILDS, SAMUEL B. Appendicitis and lesions complicating its diagnosis, deductions from x-ray examinations, *Radiology*, 1925, iv, 107-110.
- ¹⁹MOORE, A. B., and MERRITT, E. A. Roentgenological diagnosis of appendicitis, *Jr Am Med Assoc*, 1931, xcvi, 1456.

Clinical Teaching with Special Reference to Bedside Study of Disease*†

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THE word "clinical" means to lie in bed. Clinical medicine in its broadest sense means that part of medicine which has to do with the bedside investigation of disease in the living body. Clinical medicine is not a school of dogma, it is a school of method. Progress in clinical medicine is not hedged about by fixed limits, but may go as far as the individual's methods of observation and investigation can carry him.

The medical student should be impressed with this fact early in the course of his studies, because there can be no better preparation of the soil for the growth of observation, or for the budding and flowering of genius than the knowledge of an open course where all who enter the race are equally free and independent in the development of their talents.

In the middle of the sixteenth century Montanus first taught medicine by bedside instruction at Padua. He was contemporary with Vesalius, who was at this time preparing the *Fabrica* for publication, laying the foundation for modern anatomy, and giving it a place

in the curriculum which it has never lost. We may safely say that clinical teaching dates from this period at Padua, but there was little progress during a period of three hundred years.

The awakening which came in the first part of the nineteenth century ultimately placed medicine on a broad basis. Lavoisier became one of the prime movers through his discovery of the nature of respiration and the sources of animal heat. The movement gathered impetus through the enthusiastic studies in gross pathology, carried on in France by Bichat and his followers, and in Vienna by Rokitsansky and Skoda. Also through the development of percussion and auscultation by Corvisart, Laennec, Bayle, Piorry, Louis, and Andral.

While some mistakes were made and false conclusions drawn, the study of pathological anatomy and the more intelligent use of percussion and auscultation put clinical medicine forward with a bound. This was particularly true with reference to diseases of the heart and lungs. Wherever possible the symptomatic classification of disease gave place to the anatomic classification. Through these methods bedside study and observation received a great stimulus and there soon came a

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better understanding of many diseases. Laennec made his significant contributions to our knowledge of diseases of the heart and lungs; Louis through his clinical and anatomical study of disease, and his statistical and analytical methods not only made valuable additions to our knowledge, but he exerted a remarkable influence on the teaching of clinical medicine. It might be said that modern clinical teaching in America had its origin in the young American students of Louis during the fourth decade of the nineteenth century. Among these were Jackson, Shattuck, Holmes, Gerhard, Stille, Power, Flint, Swett, and Clark

With the growth of clinical medicine have come all the influences of physiology, bacteriology, physiological chemistry and the various laboratory and mechanical aids to diagnosis, all designed to supplement clinical diagnosis, yet many of them serving as a dangerous lure for the unwary student of bedside medicine. He is often tempted to think of this or that test or device as a short-cut, rather than an aid to diagnosis or a method of confirming clinical findings, and may make the fatal mistake of slighting the history of the case and omitting or abbreviating the bedside study while he awaits the laboratory report. When the report is received, it may be given unwarranted weight, because there is nothing in the scale with which its value may be checked

The bedside study of a case should begin with a carefully taken history and should not end until every organ in the body has been thoroughly examined. The true spirit of the faithful observer is expressed in the following

quotation from Louis' *Researches on Phthisis*.

"All these cases were taken on the same principles and with the same details; and as it appeared to me impossible to carry on a system of observation such as this and attend to private practice at one and the same time, I relinquished the latter altogether for the time being. I regularly passed three or four, and sometimes five hours daily in the hospital, devoting at least two hours to each postmortem examination. And although habit must have familiarized me with anatomical investigation, I still employ the same time I did two years ago in the examination. For I am convinced that if we wish to observe well, we must not observe hastily, and that the sole means of rectifying unfavorable errors is repeatedly to submit to new examination, questions which we may have at one time believed settled, and consequently to go on perpetually observing the same objects, just as if they were, in each instance, beheld for the first time"

William Harvey also possessed the spirit which should animate the true clinician when he said

"Let us then blush, in this so ample and so wonderful field of nature to credit other men's traditions only. *Nature* herself must be our adviser, the path she walks must be our walk, for so while we confer with our own eyes, and take our rise from meaner things to higher, we shall at length be received into her closest secrets"

The teacher of clinical medicine today carries a heavy responsibility. The "primal sympathy of man for man" which gave origin to medicine is being threatened by the various distracting diagnostic and therapeutic agencies, which, through spectacular appeal, or the promise of a short-cut, tend to draw the student away from the bedside

While our knowledge of disease and its treatment has been greatly aug-

mented in the past century, and while this increased knowledge has materially altered our diagnostic methods and our therapeutic procedures, it has in no way altered the relation of host and disease. Human nature is just the same: disease untreated, works the same ravages in the human organism. The need of sympathetic understanding is still eminent. The clinical teacher must cultivate the *art* of medicine, his manner must be such as to inspire confidence and hope, and yet "the seeing eye, the hearing ear, the sensitive fingers and the understanding mind" must be employed with such searching effect that they approach the accuracy of a science. With these qualifications the teacher of clinical medicine should stand in relation to the student as a guide at the threshold of this most intricate and interesting unit of society, the human organism, ready to acquaint him with the normal living anatomy and physiology, prepared to elicit the history of disease, ready to demonstrate the methods of physical exploration for the purpose of discovering departures from the normal, quick to sense mental and psychological deviations, trained in the correlation and diagnostic appraisal of facts obtained; generous but discriminating in the use of laboratory and mechanical aids, and finally conservative and humane in the application of treatment. I think this is not too much to ask of the clinical teacher, the more he brings to the bedside, the more he will take away.

The student can be interested in the methodical demonstration of the normal and the discovery of departures from the normal. It is a mistake to

allow him to go through medical school with the impression that if he learns anatomy, physiology, biological chemistry and bacteriology he will then be suddenly endowed with so-called diagnostic instinct, or as Oliver Wendell Holmes says "intuitive sagacity". He must learn that intuitive sagacity is synonymous with hard discipline and that every individual is endowed with special senses which if properly trained, may become powerful instruments of precision, incredibly keen and penetrating in their search of knowledge, and to go on the trail of disease with such weapons is like playing an interesting game.

Doctor Henry A. Christian has said

"Perhaps the fault of the student is, more than we admit, a reflected fault of the teacher. We are constantly criticized through our students' work by their plunging immediately into instrumental and laboratory methods of examination of patients. Is not that the thing that we are doing ourselves a great deal more than we should, if we remember that we stand before our students as exemplars? Are we not too much inclined to fail to commit ourselves definitely to a certain finding as normal or abnormal after simple methods of examination? I am very sure that I am guilty often in that respect, notwithstanding that I rather carry it on my conscience to be guiltless as far as possible. As teachers we refer too readily to the x-ray or examinations of that special sort. I do not mean at all to decry reference to the x-ray, but we refer the patient for special examinations before we commit ourselves in the presence of the students to our judgment about the matter based on history and simple methods of examination. It seems to me we need to go over our patients with our students, using simple methods of examination, as soon as they come into the clinic or into the hospital, put down what we find, draw a conclusion, and then let other methods check up. It is not necessary, then, to argue with the student either the

merits or the limitations of the simple method. You are shown to be correct or incorrect, and in time the student will learn both your ability to use simple methods of examination and your failures in so far as your limitations are set by these other methods."

With these facts in view it would seem wise for medical school curricula to offer more bedside instruction and

less amphitheater surgery. May the spirit of such men as Sydenham, Boerhaave, Laennec, Allbutt, and Osler inhabit the wards of every teaching hospital in order that the simple methods of bedside investigation may be preserved and that the knowledge of clinical medicine may reach its ultimate refinement!

Wastage of Health and Money in Sectarian Cults

"THE objection to the existence of sectarians is not so much that their therapeutic methods are in themselves incorrect as that the use of these or any other therapeutic measures by individuals untrained in the medical sciences, unable to diagnose disease, and unaware of their own limitations, is unsound, dangerous, and economically wasteful. It is established beyond doubt that in some disease conditions cures may be effected through the prompt employment of the appropriate remedial measures—early surgical intervention for cancer and acute appendicitis, antitoxin for diphtheria, quinine for malaria, salvarsan for syphilis, etc. Delay in the diagnosis of these conditions and in the employment of the proper remedy may result in a more serious illness than might otherwise occur, or may even result in death. There is danger not only to the individual but also to the community. How foolish it is for a community to maintain an elaborate public health machinery to prevent the spread of certain communicable diseases, and yet permit individuals to practice who are unable to differentiate diphtheria from pneumonia or scarlet fever from measles. In experimenting with sectarians, people often spend large amounts of money which they can ill afford."

From *The Healing Cults—A Study of Sectarian Medical Practice Its Extent, and Control*. By LOUIS S. REED, PH.D. The Committee on the Costs of Medical Care, 910 Seventeenth Street, N.W., Washington, D.C.

Editorials

DEATH FOLLOWING THE USE OF ACETYLSALICYLIC ACID IN ASTHMATIC CONDI- TIONS

Notwithstanding the growing literature with constantly multiplying reports which detail serious untoward effects and even death following the use of acetylsalicylic acid in attempting to obtain relief from asthmatic conditions, further emphasis of this danger is indicated. An illustrative case is to be found in this issue of the *ANNALS*. In Case I of the group of patients described by Dr Macdonald¹ it had been noted on several occasions that severe attacks of asthma had followed the administration of coal-tar products. Finally, one-half hour after taking 10 grains (0.6 gm) of aspirin, the patient suffered a severe attack of asthma in the course of which death occurred. In discussing the etiology of this condition, Macdonald gives a brief review of earlier reports of similar fatalities, and calls attention to the fact that it is altogether out of the question to attribute the fatal outcome under such circumstances to the toxicity of acetylsalicylic acid in the ordinary sense of the term. He quotes de Jankovich on this point to the effect that the lethal dose can be fixed at 20 gms. The ill-effects which have been observed following the ingestion of but 5 or 10 grains (0.3 to 0.6 gm) must have an allergic basis.

A recent coroner's case in the experience of the writer apparently falls in this group. A robust-appearing young man consulted a druggist for symptoms which he believed indicated a "cold". He was given two remedies of which one was acetylsalicylic acid in 5 gr tablets. He took two of these tablets before leaving the store. Whether he took others is not known. Several hours later he was found in bed extremely dyspneic and cyanotic, and died before a physician could be obtained. Attention is called also to the recent paper by Lamson and Thomas² describing four examples of allergic response, one fatal, following the use of a nostrum for the treatment of asthma, the chief ingredients of which are acetylsalicylic acid and caffeine. The frequency of such ill-effects might lead to the impression that in some way a synergistic effect exists between the asthmatic state and acetylsalicylic acid. Rather must we recognize the pathologic constitution (thymico-lymphatic) which is the common substrate for the allergic response in both instances.

It is indeed with truth that Walzer³

¹MACDONALD, I. G. The local and constitutional pathology of bronchial asthma, *ANN INT MED*, 1932, 11, 253-277.

²LAMSON, R. W. and THOMAS, R. Some untoward effects of acetylsalicylic acid, *Jr Am Med Assoc.*, 1932, 101, 107.

³COCA, A. F., WALZER, M., and THOMAS, A. A. Asthma and hay fever, Charles C. Thomas, 1931, p. 280.

wrote "Aspirin and the closely related coal-tar products are among the most treacherous drugs employed in the therapy of asthma. Their routine or careless prescription for atopic patients is a dangerous practice"

CARDIAC HISTOPATHOLOGY IN THYROTOXICOSIS AND ADENOMATOUS GOITER

Whether there are characteristic histopathological changes, or any changes at all for that matter, in the hearts of patients who have shown clinical evidences of cardiac disturbances in association with thyrotoxicosis has been subject to much difference of opinion. The staff of the Department of Pathology has recently conducted a purely objective investigation of this problem, a preliminary report of the results of which is to appear in a forthcoming number of the *American Heart Journal*. In connection with other lines of investigation which are described in that report, from a total of 43 autopsies of cases of exophthalmic goiter, 35 were selected as being free from evidences of syphilis, rheumatic fever, infective endocarditis or severe coronary atherosclerosis so that as far as possible known causes of myocardial changes were eliminated. A control series was then set up by matching each individual case of the exophthalmic series with another of the same age and sex, i e., with a case as similar as possible in all respects except that exophthalmic goiter had not been present. Comparable microscopical slides from the hearts of these 70 cases were then examined and the results tabulated as to thirteen items commonly made note of in such examinations of the heart wall. In compar-

ing the two series by this method only four features were found to occur with sufficiently greater frequency in the exophthalmic series to suggest that they might be significant. These were myocardial hypoplasia, fibrosis of the myocardium, endocardial sclerosis and cellular infiltrations. Myocardial hypoplasia was judged largely by the state of the muscle of the right ventricle. Its significance is that of constitutional pathology, vascular hypoplasia being a constant finding in the Graves' constitution.

Of the hearts in the exophthalmic series, 80 per cent showed myocardial fibrosis as compared with 51.5 per cent in the control series. The areas of fibrosis were usually small and were found chiefly in the left ventricular wall and the papillary muscles. The type of the fibrosis was such that it could not have been due to arteriolar occlusion. In four instances cellular infiltrations associated with patchy fibrosis were found, but in none of these were early lesions of the muscle fibers themselves seen, and the wandering cells were relatively few. In one case only was there a severe active myocarditis of the type described by Fahr. In this heart there were many focal lesions occurring throughout the myocardium, even in the auricles. These lesions were non-purulent and were present in all stages of a series extending from focal necroses with lymphocyte and plasma cell infiltrations to old and somewhat hyaline patches of fibrosis. As far as histopathological study could determine, such changes as were present in this heart would be entirely capable of leading to the areas of fibrosis found in a large proportion of the

exophthalmic series. If such was their etiology, it is difficult to understand why, in such a relatively large series, only a single example should be found in a stage of noteworthy activity. Nevertheless, no other etiological factor than the hyperthyroid state could be found for that particular case.

The hearts of 55 cases of adenomatous and nodular colloid goiter were compared by the same method with a matched control series from non-goitrous individuals. No significant difference in the incidence of pathological changes could be discovered between the two series.

Abstracts

Über das Auftreten von Perikarditis nach Lungeninfarkten [The Occurrence of Pericarditis Following Pulmonary Infarction] By PAUL WERMER (Klin Wochenschrift, 1932, xi, 329-330)

The deplorable frequency of both spontaneous and post-operative venous thrombosis and pulmonary embolism in recent years has directed attention to the etiology and pathogenesis of pulmonary infarction, and justifies description of a clinical picture which the author believes has not previously been detailed—pericarditis resulting from infarction of the lung. The etiology of this condition is considered to be direct extension of the fibrinous pleuritis which is always found over the base of an infarct to the pleuropericardial layer (pericarditis externa) and then to the visceral pericardium. Characteristic cases are presented. In making the diagnosis the evidences of the initial pulmonary pathology will usually be clearcut. The sudden appearance of stabbing pain in the side, cough and dyspnea, after an operative procedure, together with evidences of collapse, pallor or cyanosis, tachycardia, and thin feeble pulse make the diagnosis of embolism of a small pulmonary artery extremely evident. To this picture the evidences of a pericarditis are added in the syndrome under consideration. Pericarditis having this etiology was characterized in the author's cases by the roughness of the friction sound, by its fugacity and by the severe pain in the cardiac region which was readily distinguishable from the

pain produced directly by the infarct. Differential diagnosis between this and other forms of pericarditis is discussed. Since pulmonary infarction at times gives no clinical signs or symptoms, in the association of the two conditions here described may be found the cause of some examples of "idiopathic" pericarditis for which no explanation has hitherto been available.

The Amount of Epinephrin in Extracts of the Medulla, Cortex and Whole Suprarenal Gland of Rabbits, Pigs, Cattle, and Horses By TAKEO KOZIMA, MAMORU NEMOTO, SHIZUKA SAITO, HIROSHI SATO, and TAISUKE SUZUKI (The Tohoku Jr of Exper Med, Sendai, Japan, 1932, xix, 205-232)

Extracts were made from the medulla, cortex and whole substance of suprarenal glands of oxen and horses, of the medulla and whole glands of pigs, and of the whole gland of rabbits. The epinephrin content of these extracts was estimated by means of the colorimetric method of Fohn, Cannon and Denis, that of Suto, the rabbit intestine segment method, the blood pressure of the pithed dog, the cat paradoxical pupil reaction, the perfusion of toads' legs and rabbits' ears. The results obtained are presented in tabular form. The suprarenal gland of the horse gave similar values for epinephrin regardless of the methods applied, but the glands of rabbits, pigs and cattle gave variable results in respect to the methods used, and the character of these

variations differed with the various species as well. To explain these variations, which are confidently believed not to depend upon technical error, certain suggestions are made. It is possible that the active principles in the extracts should not be assumed to be adrenalin alone, but some mixture of adrenalin and allied substances. Or, extracts may contain besides adrenalin some substances which act to intensify the action of epinephrin in various degrees according to the test object employed. Perhaps both of these alternatives act together. As previously recorded, there was demonstrated in small amount in the adrenal cortex of cattle and horses that substance which gives a positive reaction to the Folin test but none to the Suto test or to the biological tests.

Observations on Heart Sounds with Particular Reference to Gallop Rhythm and Sounds of Auricular Origin By A. GARRARD MACLEOD, FRANK N. WILSON and PAUL S. BARKER (Proc Soc Exp Biol and Med, 1932, xxix, 1009-1010)

Two Einthoven galvanometers coupled in tandem were used to record the electrocardiogram and the heart sounds simultaneously, and the electrical stethoscope manufactured by the Western Electric Company was used to convert the sounds into electrical variations. The study of a large number of phonocardiograms led to the following tentative conclusions. From the graphic standpoint gallop rhythm may be defined as a condition in which three sounds occur during each cardiac cycle. Several varieties may be distinguished: (a) Protodiastolic gallop rhythm in which the extra sound follows the second heart sound by a constant interval and occupies the same position in the cardiac cycle as the normal third heart sound. (b) Presystolic gallop rhythm in which the extra sound precedes the first heart sound by a constant interval,

and is almost certainly of auricular origin. The onset of the extra sound falls within the P-R interval of the electrocardiogram. This appears to be the most common type of gallop rhythm. It is particularly frequent in cases of arterial hypertension. (c) Systolic gallop rhythm in which the extra sound falls within the limits of ventricular systole. This type of gallop rhythm is uncommon and apparently has no clinical significance. (d) Gallop rhythm due to audible auricular sounds when the P-R interval of the electrocardiogram is increased beyond normal limits in which case the extra sound may fall in any part of diastole. This should probably be considered a variety of presystolic gallop rhythm.

Production of Thyroid Hyperplasia in Rats and Mice by Administration of Methyl Cyanide By A. W. SPENCE and DAVID MARINE (Proc Soc Exp Biol and Med, 1932, xxix, 967-968)

The senior author and his associates have shown previously that the daily subcutaneous administration of small doses of aliphatic cyanides to young rabbits of either sex, maintained on a diet of alfalfa hay and oats, will produce thyroid hyperplasia within 21 days. Methyl cyanide was found to be most potent in this respect. Rats were given daily subcutaneous injections of varying doses of methyl cyanide in water. After 21 days only very slight thyroid hyperemia was shown. After 28 days there was definite thyroid hypertrophy, but it was obvious that the thyroid of the rat was less reactive than that of the rabbit. With increased dosage for the intervening days the thyroids were larger and more hyperemic at the end of 36 days. Although there were individual variations, in general the thyroid reaction was proportional to the dosage. Only a slight thyroid reaction was produced in mice after periods of dosage of from 11 to 34 days.

Reviews

Surgery of the Chest By GEORGE F STRAUB, M D, F A C S xx + 475 pages, 341 illustrations, including 68 in color Charles C Thomas, Springfield, Illinois 1932 Price, \$10 50 postpaid

Although outside of the field of practice of most of the readers of the ANNALS, it is appropriate to give brief mention to this book. There is perhaps no other anatomical area for specialization in which community of knowledge is more essential on the part of the internist and surgeon than the thorax. Since this book presents the recent advances in this field and discusses the application of surgical methods to a considerable number of diseases usually first seen by the internist, this treatise must be of interest and value to that group. For the surgeon it describes technical procedures as well. Not only is this book well written but it gains much from its numerous illustrations, many of which are reproduced from drawings by the author. Skillful use has been made of an additional color in many of the figures. The format is excellent.

Lang's German-English Dictionary of Terms Used in Medicine and the Allied Sciences with their Pronunciation Revised and edited by MILTON K MYERS, M D, Neurologist to the Northern Liberties Hospital, Chief of Nerve Clinic, St Agnes Hospital, Consulting Neurologist, Jewish Hospital, Philadelphia, etc. Fourth edition, enlarged 926 pages P Blakiston's Son and Company, Philadelphia Price, \$10 00

Practically every English-speaking reader of medical German, not born to the language, has made use of the earlier editions of Lang's German-English Dictionary of medical terms. Such a dictionary is, in fact, indispensable. The standard German-English dictionaries lack all except the more frequently used medical terms and cannot

give the specific medical significance of many terms which have a common usage as well. This new edition has been entirely reset. This was made necessary by the addition of the pronunciation, in easily understood English syllables, of each word. Also 3,500 new words have been added, bringing the total to approximately 56,500 definitions. This gives a work which is not only satisfactory for the general reader of medical German but also an important aid to the translator or researcher. This new edition will be welcomed by the users of its predecessors. German remains the most important foreign language for the English-speaking physician.

Biochemistry in Internal Medicine By MAX TRUMPER, Ph D, Clinical Chemist and Toxicologist, formerly in charge of the Laboratories of Biochemistry of the Jefferson Medical College and Hospital, and of the Psycho-Biochemistry Laboratory, Graduate School of the University of Pennsylvania, and ABRAHAM CANTAROW, M D, Instructor in Medicine, Jefferson Medical College, Assistant Attending Physician, Philadelphia General Hospital, in charge of Laboratory of Biochemistry, Jefferson Hospital, with a foreword by ELMER H FUNK, M D, Sutherland M Prevost Professor of Therapeutics at Jefferson Medical College 454 Pages, 11 figures W B Saunders Company, Philadelphia 1932 Price, in cloth, \$5 50 net

This book is designed to correlate the established facts of biochemistry with the ordinary diagnostic problems of internal medicine. It is not a laboratory manual and accordingly is not concerned with the details of laboratory procedures. Rather it aims to give the clinician a clear understanding of the significance of the results of laboratory investigations within the field of biochemistry and related sciences. First

chapters are devoted to consideration of the clinical aspects of fundamental metabolic processes in health and disease. Then follow ten chapters dealing with more highly specialized functions and the biochemical aspects of certain disease states. The final chapter is an outline of the chemical diagnostic features of various disorders, thus providing an indexed table of the clinical laboratory tests of a chemical nature which are informative in various disease conditions. The style is lucid, and highly technical discussions and matters which are yet largely controversial are omitted. Free use of section and paragraph headings in several styles of type emphasizes the logical arrangement. This is a well made book which promises to be very useful.

Physiotherapy Its Principles and Practice

By F. HOWARD HUMPHRIS, M.D. (Brux.), F.R.C.P. (Edin.), M.R.C.S. (England), D.M.R. and E. (Camb.), Hon. Consulting X-ray Physician and Electrotherapist to Christ's Hospital, Hon. Consulting X-ray Physician and Electrotherapist to the London Clinic, Late Officer in Charge X-ray and Electrotherapeutic Departments, 3rd London General Hospital, Capt. R.A.M.C. (T.F.), Late Consulting X-ray Physician to the Force in Egypt, Major R.A.M.C., Past President of the American Electrotherapeutic Association, Past Vice-President of the Section of Electrotherapeutics, Royal Society of Medicine, and RALPH E. STUART-WEBB, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P., with contributions by FRANK ROMER, M.R.C.S., L.R.C.P., A. E. HAYWARD PINCH, F.R.C.S., M.R.C.P. and A. GORDON WATSON, M.D. The Macmillan Company, New York, 1932. Price, \$4.50.

Physiotherapy, as its full title indicates, is divided into two parts. In the introduction the author defines Physiotherapy as "the treatment of the patient by physical means, at the hands of the physician or by the art and skill of the surgeon" and he stresses the necessity of physiotherapists being medically trained. In the first part, "Principles", a very full and detailed description of the application and apparatus of the various physiothera-

peutic agents is given, as well as a brief historical review of the older methods, such as static electricity and low and high voltage currents. Infra-red rays, being antagonistic to ultra-violet and X-rays, may be used to some extent as preventive and curative of X-ray lesions, it is stated.

"Radium Therapy", which is Dr. Pinch's contribution, is a chapter of but 17 pages. One may well question the wisdom of attempting to present such an important subject in so small a compass. Ample warning is given as to possible complications and sequelae.

"Massage and Manipulation" by Dr. Frank Romer is well done. He wisely urges medical men to be sure that they give their patients no reason for going to a "bone setter". A doctor should know how to prescribe massage, and what particular cases need it. X-ray plates should be made of joints, before manipulation, to make sure that no pathological lesion exists.

Because in this country spa treatment is less known and less popular than in England and on the Continent, the discussion of this method of physiotherapy is of interest. One wonders, however, about the wisdom of the inhalation of radio-active waters over several days, in view of recent knowledge of the effects of fixation in the skeleton. Dr. Watson aptly states that "all mineral waters cure some cases", although he feels that at present the claims of spas are too conservative. Quite naturally he stresses the advantages of the British spas. Melted paraffin-wax baths and foam therapy are less common physiotherapeutic agents.

Under "Practice" the use of physiotherapy and what may or may not be accomplished in various disturbances and diseases is considered. One feels that some statements of the results seem at times over-enthusiastic, but the gratifying effects in poliomyelitis we know are not exaggerated. Particularly interesting is the description of Krowler's method in the treatment of tuberculous laryngitis, "in which the patient himself directs a beam of sunlight down his own throat by means of an ordinary looking-glass and a laryngoscopic mirror, for about an hour a day". This has been used by some laryngologists in this country with

decidedly good results. Dermatological use of physiotherapeutic agents is so general as to require no comment. The last chapter on the treatment of "Various Diseases" is of some present day importance to the devotee of sports, as golfer's back, motorist's heel, rider's strain and tennis elbow are all optimistically treated.

Throughout, the author insists that the physiotherapist cooperate with the physician and surgeon. The book is of general interest and value to all practitioners, and of real practical assistance to one whose special field is physiotherapy.

R C W

Conquering Arthritis By H M MARGOLIS, M D, x+192 pp, 3 illustrations. The Macmillan Co., New York City, 1931. Price, \$2.00.

"Conquering Arthritis" is the somewhat optimistic title of another of the growing stream of books written for certain classes of patients by specialists in the particular disease discussed. Readily comprehensible to the intelligent reader and written by experts without the bias of commercial interests, they do much to aid the physician in his professional duties and may prove to be invaluable to his patients. Faced with a problem made unusually difficult not only by its own complexities and uncertainties but also by the necessity of using non-technical phraseology, the author has produced a work which, with a minimum of dogma, succinctly and unemotionally states the present knowledge of the genesis and treatment of arthritis. After a brief review of the history of the disease, the discussion of chronic arthritis is introduced by a simple classification, the following forms being recognized: (1) Senescent arthritis, (2) static arthritis, (3) metabolic arthritis, and

(4) infectious arthritis. Each of these forms is treated separately but the greater portion of the book is devoted to the fourth class, with a somewhat extended discussion of the relation of focal infection to inflammation of joints. Especial emphasis is placed upon the teeth and tonsils as foci of localization of streptococci. While the author treats this subject quite dispassionately, nevertheless the uncritical reader might well receive the impression that laboratory animals may show arthritic changes when injected with organisms from human focal infections irrespective of the mode of injection and further, that such changes, when they occur, constitute proof of the existence of arthrotropic organisms. The author considers the patient's genetic background exceedingly important in the etiology of chronic arthritis. Stress is laid upon various forms of treatment and the necessity for adjusting the therapeutic measures to the patient as well as to the known or surmised etiological factors. Margolis feels that available therapy is of great value even in advanced cases. Dietary, physiotherapy, and medicinal procedures are explained with conservative opinions as to probable results. This phase of the subject is developed very well, for although much information relative to treatment is given, there is nothing which would tend to induce or enable a patient to treat himself without the advice of his physician. Just as manuals on diabetes mellitus, on nutrition, and upon other subjects have served to bring the physician and his patient into a clearer understanding of their mutual problem, so this book should be of distinct value in the treatment of intelligent patients with chronic arthritis.

J C B

College News Notes

Dedicatory exercises for the new Medical Laboratory Building of the University of Texas, the John Sealy Hospital Outpatient Building and the Rebecca Sealy Residence for Nurses were held at Galveston, May 30-31, 1932. Dr George E Bethel (Fellow), Galveston, delivered the address of welcome. Dr M L Graves (Fellow), Emeritus Professor of Medicine of the University of Texas, presented two clinics, and Dr L F Barker (Fellow), Emeritus Professor of Medicine at the Johns Hopkins University School of Medicine, gave a medical clinic.

Mrs Helen Felch Jennings, wife of Dr Charles Godwin Jennings (Master and Second Vice President of the College), died suddenly immediately following the San Francisco Clinical Session. Mrs Jennings was a daughter of Alpheus Felch, Fourth Governor of Michigan, a descendant of one of the early settlers of that State.

Dr Walter A Bastedo (Fellow), New York, Dr Oscar Bethea (Fellow), New Orleans, Dr Charles L Brown (Fellow), Ann Arbor, Dr Henry Christian (Fellow), Boston, Dr Bernard Fantus (Fellow), Chicago, and Dr Virgil E Simpson (Fellow), Louisville, attended a meeting at Philadelphia, April 30, as members of the Sub-Committee on Scope of the United States Pharmacopoeia Revision Committee. This Committee is now selecting the newer remedies for the Pharmacopoeia. Many of these are patented, and over such the Pharmacopoeia can exert no control. As their titles and descriptions are legalized, the Committee can make such a remedy official only if the patentee agrees to every word of the text used by the Pharmacopoeia and agrees to abide by the standard so set for his product. In many cases, this agreement is refused. In some cases where it is accepted, manufactur-

ers of allied products claim an equal right to a place in the Pharmacopoeia, on the ground that pharmacopoeial recognition of only one member of a class would be unjust discrimination and would afford an unfair advertising opportunity.

Dr F M Pottenger (Fellow and President of the College), Monrovia, Calif, gave an address at the annual meeting of the State Medical Association of Texas at Waco, Texas, May 7, 1932, on "The Relations of Tuberculosis to General Medicine".

The Central Tri-State Medical Society, composed of physicians of Kentucky, Ohio and West Virginia, recently conducted its annual meeting. The entire scientific program was offered by Fellows of the College, as follows:

Dr Walter Freeman, Washington, D C
—"Conservative Treatment of Head Injuries",

Dr J Shelton Horsley, Richmond, Va—"Cancer of the Stomach",

Dr Charles H Cocke, Asheville, N C
—"Certain Phases of the Healing Process of Tuberculosis".

Dr Louis F Bishop (Fellow) and Dr Louis F Bishop, Jr (Fellow), both of New York City, took part in the scientific exhibit at the meeting of the American Medical Association, New Orleans, May 9-13. Their exhibit consisted of electrocardiograms with descriptive titles on Vertigo and Syncope in Cardiac Arrhythmias.

An examination of the Program of the annual meeting of the American Medical Association discloses that eighty-nine Fellows and four Associates had official assignments.

Dr J Burns Amberson, Jr (Fellow), Assistant Professor of Clinical Medicine,

Columbia University College of Physicians and Surgeons, was the guest lecturer and delivered a didactic lecture each day, followed by bedside instruction, in connection with the Five-Day Postgraduate Tuberculosis Institute League at the Jersey City Medical Center, May 16-25, under the joint auspices of the Hudson County Medical Society, Hudson County Tuberculosis League and the Hudson County Tuberculosis Sanatorium and Clinics. Dr. Amberson's subjects were Pathology and Pathogenesis.

Dr. Asher A. White, son of Dr. S. Marx White (Fellow and Ex-President of the College), has been awarded the Alexander Cochrane Bowen scholarship in medicine, and will spend next year with Dr. Francis R. Fraser. The scholarship affords opportunity for one year postgraduate study and research at St. Bartholomew's Hospital in London. Dr. White received his M.D. degree from the University of Minnesota in 1929. He was interne and then resident in the New York Hospital for two years with Dr. Lewis A. Conner (Fellow) and Dr. Nellis Foster.

Dr. William H. Walsh (Fellow), Chicago, has been selected as the Medical Consultant of a new Medical Center at Monterrey, Mexico, by the Governor and Secretary of the State of Nuevo Leon. The new Medical Center contemplates a new medical school, a general hospital of five hundred beds, a nurses' home, a separate wing for tuberculosis, one for the insane, and another for communicable diseases. Dr. Walsh was formerly Executive Secretary of the American Hospital Association, and is now engaged in hospital planning, organization, management and equipment.

Dr. Frederick J. Farnell (Fellow), Providence, R. I., Chairman of the Public Welfare Commission of the State of Rhode Island, is the author of the following articles which appeared recently in the United States Daily

"Task of Reshaping Characters of Paroled Convicts",

"Conflict of Prison Industries with Products of Free Labor",

"Sanitation as Crime Preventive"

Dr. Frank Parsons Norbury (Fellow), Jacksonville, Ill., was initiated to honorary membership in the Illinois Epsilon Chapter of Phi Beta Kappa fraternity recently. Dr. Egerton L. Crispin (Fellow), Los Angeles, Calif., is a member of the Alumnus Membership Committee of this national honorary fraternity.

The obituary notice for Dr. John Alden Lichty which appeared in the July issue of the Annals was prepared by Dr. Clement R. Jones, Regent. Through oversight the usual acknowledgement was not made.

Dr. Wann Langston (Fellow), Oklahoma City, Okla., appeared on the circuit postgraduate course of the University of Oklahoma, Extension Department, June 13-15, lecturing on the subject "General Vascular Disease, Hypertension and Myocardial Disease" at Clinton, Elk City, Woodward and Alva, Okla.

Dr. J. W. Torbett (Fellow), Martin, Texas, addressed the North Texas Medical Association at its regular semi-annual session at Bonham, Texas, on June 15 on the subject "The Intradermal Use of Bacterial Antigens for the Diagnosis and Treatment of Several Chronic Diseases". Dr. Torbett read a paper before the State Medical Association of Texas at its May meeting in Waco on the subject of "Peribronchial Glands as a Focus of Systemic Diseases".

Thurman Delna Kitchin (Fellow), Wake Forest, North Carolina, President of Wake Forest College, was recently appointed by Governor O. Max Gardner of North Carolina a Member of the Commission for the Improvement of Laws. In May of this year, Dr. Kitchin became a member of the Duke (Rho) Circle of Omicron Delta Kappa, and on June 8, 1932, the LL.D. degree was conferred upon him by Duke University.

Dr. Ray M. Balcutt (Fellow), Oklahoma City, addressed the Twin Lakes District Medical Society, Rockwell City, Iowa at its Tenth Annual Assembly, June 16, on the subject of "Diagnosis and Treatment of Allergic Diseases".

Acknowledgement is made of the following gifts to the College Library of publications by members

Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,
 Dr Algernon B Jackson (Fellow), Washington, D C—4 reprints,
 Dr H R Livengood (Fellow), Elizabeth, N J—1 reprint,
 Dr Robert U Patterson (Fellow), Washington, D C—1 reprint,
 Dr Clair L Stealy (Fellow), San Diego, Calif—1 reprint,
 Dr Samuel Weiss (Fellow), New York, N Y—1 reprint

Dr Robert U Patterson (Fellow), Surgeon General of the U S Army, was the recipient of the honorary degree of Doctor of Laws bestowed by his Alma Mater, McGill University, at the annual Convocation of that institution for the conferring of degrees on May 26, 1932

Dr Rock Sleyster (Fellow), Wauwatosa, Wis, was re-elected a member of the Board of Trustees of the American Medical Association for five years, during the New Orleans meeting, May 12

Dr C W Greene (Fellow), with Dr Frank A Hartman, Dr J J Maisel and Dr G W Thorn, all of the University of Buffalo, were awarded the gold medal by the Committee on Awards of the American Medical Association in connection with the scientific exhibit at the New Orleans Session, "for original investigative work on the development and use of a hormone from the suprarenal cortex and excellence of presentation"

Dr J Arnold Borgen (Fellow), Dr P W Brown (Fellow), with Dr H M Weber, of the Mayo Clinic and Foundation, Rochester, Minn, were awarded the bronze medal, "for original investigation of diseases of the colon and excellence of presentation"

Dr Ross V Patterson (Fellow), Dean of Jefferson Medical College of Philadelphia, was honored, June 13, by Colgate Uni-

versity with the degree of Doctor of Science

Dr Mary O'Malley (Fellow), Washington, D C, was elected President-Elect of the Medical Women's National Association at the annual meeting of that Society in New Orleans, May 9

Dr Herbert L Bryans (Fellow) Pensacola, Fla, was recently reappointed a member of the Committee on Publication of the Journal of the Florida Medical Association

"A New Non-surgical Method of Treatment for Gastric and Duodenal Ulcer" was the subject of an address delivered by Dr L Winfield Kohn (Fellow), New York, before the New York State Medical Society's meeting at Buffalo, May 25, 1932

Dr Edward J Engberg (Fellow), St Paul, Minn, was re-elected Secretary of the Minnesota State Board of Medical Examiners for the term of one year, at the May meeting of the Board

Dr Ralph deBallard Clarke (Fellow), Meriden, Conn, presented a popular public lecture on May 4 on the subject of "What is New in Tuberculosis" to a group comprising parent-teachers' organizations, public health association members, classes from the Nursing School of the Meriden Hospital, and the general public. Compression therapy and collapse surgery were illustrated by X-ray films, as they were applicable to a series of tuberculous children and adolescents

Dr Joseph Rogers Darnall (Fellow), Major, Medical Corps, U S Army has been awarded the Order of the Purple Heart. Major Darnall was wounded in action during the Meuse-Argonne offensive, October 28, 1918. Major Darnall also received a departmental commendation for his foresight and work in preventing a possible epidemic during the emergency occasioned by water shortage in Zamboanga, P I, while he was stationed there as Surgeon in 1928

Dr Hyman I Goldstein (Associate), Camden, N J, read a paper entitled "Recent Ad-

vances in Treatment, Hemorrhagic Diseases, Anemias, Uremia and Dropsy, Muscular Dystrophies, Diphtheria, Chorea and Meningitis" before the Medical Society of New Jersey at its annual meeting in Atlantic City, June 16, 1932

Dr Elliott P Joslin (Fellow), Boston, Mass, addressed the annual meeting of the Fifth Councillor District of the Medical Society of the State of Pennsylvania at York, July 28, on diabetes

Dr Ada E Schweitzer (Fellow), Indianapolis, Director of Infant and Child Hygiene on the Indiana State Board of Health, conducted a Child Health Institute, Winona Lake Chautauqua, July 3 to 9, inclusive. The program was devoted to home protection and to the conservation of the child by the home in cooperation with the community and with organized lay groups and professional and official agencies

Dr Waller S Leathers (Fellow), Nashville, Tenn, was re-elected President of the Nashville Board of Medical Examiners for the coming year, during their annual meeting at Washington, May 2

Dr Alvin G Foord (Fellow), Pasadena, Calif, was made President-Elect of the American Society of Clinical Pathologists at its meeting in New Orleans, May 6-9

Dr William H Robey (Fellow), Boston, Mass, was recently elected President of the Suffolk District Medical Society

Dr Henry F Stoll (Fellow), Hartford, Conn, was elected President of the Hartford County Medical Association at its one hundred and fortieth annual meeting on April 5, 1932

Dr Cecil Lorio (Fellow), Baton Rouge, La, was made President of the Louisiana

State Pediatric Society at its meeting in New Orleans, May 10

THE 1932 GRADUATE FORTNIGHT OF

THE NEW YORK ACADEMY OF MEDICINE

Tumors, benign and malignant, will be the theme of the 1932 Graduate Fortnight of the New York Academy of Medicine to be held Oct 17-28. The medical profession of the country is invited to participate in the intensive two week study of this important medical and surgical subject. A full program of clinical demonstrations, lectures and conferences has been arranged to cover all phases of tumors, their diagnoses and treatment.

Concurrent with the Fortnight, and for an added week thereafter, there will be housed in the Academy building an exhibition of anatomical specimens numbering approximately 3000 units. A number of the sections in the exhibition will be subjected to lecture demonstrations at regular intervals.

Ten evening meetings have been arranged during which tumor growths in various parts of the human anatomy will be discussed. Among the speakers are included Doctors W Gordon M Byers, Edwin Beer, Charles A Elsberg, James Ewing, Donald C Balfour, Daniel F Jones, Dean Lewis and Francis Carter Wood.

Thirty afternoon clinical meetings and demonstrations have been arranged in eighteen of New York City's leading hospitals, including Bellevue, Lenox Hill, Presbyterian, St Luke's, Fifth Avenue, Post-Graduate, Neurological Institute and others.

There is no charge for attendance at any of the clinics or meetings, but registration is required for participation in the hospital demonstration clinics. A complete program and registration blank for the clinics and demonstrations may be secured by addressing The New York Academy of Medicine, 2 East 103rd Street, New York City.

OBITUARIES

DR LEONARD F C WENDT

Dr LEONARD F C WENDT (Fellow), Detroit, Michigan, died suddenly June 11, 1932, of heart disease at the age of 56 years

Dr Wendt was born in Detroit, the son of Henry R and Julia Wendt. He graduated from Baldwin University, Berea, Ohio, in 1896, receiving the degree of Bachelor of Sciences, and from the Detroit Homeopathic College in 1902, receiving the degree of Doctor of Medicine. He received the honorary degree of Doctor of Science at Baldwin University in 1928.

Dr Wendt was Chief of the Diabetic Clinic at Grace Hospital, Detroit, for fifteen years. He was also a member of the Executive Board of that hospital. During the World War he was Secretary of the local Medical Advisory Board, as well as its examiner. He was Grace Hospital's volunteer physician at Camp Custer. At one time he taught diagnosis and pediatrics at the old Detroit Homeopathic College, and during 1915 was Instructor in Physical Diagnosis in the Detroit College of Medicine and Surgery. He was Consulting Physician at Miriam Memorial Hospital and Attending Physician to the Eloise Hospital for Mental Diseases. Dr Wendt was the author of several monographs on diabetes.

He will be remembered for many years to come for his work among diabetic children. In their interest, he established a summer camp on a lake near Brighton, Michigan, in 1926. He continued this project each year with the help of the Red Cross and of Grace Hospital, but at great expense

to himself personally. Many children from Detroit and other parts of the State, who otherwise might have had to suffer their affliction in the heat of the city, have been greatly benefited. The camp will be continued and will be known as the Leonard Wendt Camp for Diabetic Children.

Dr Wendt was a member of the Wayne County Medical Society, the Michigan State Medical Society, a Fellow of the American Medical Association, a member of the Interstate Medical Society, the Michigan Trudeau Society, the Society for the Advancement of Science, and the Association for Internal Secretions. He had been a Fellow of the American College of Physicians since 1920.

(Furnished by WILLIAM M LEFEVRE, M D, F.A.C.P., Muskegon, Michigan)

DR FREDERICK WILMOT MANN

Dr FREDERICK WILMOT MANN (Fellow), Houlton, Maine, died June 16, 1932, at the Aroostook Hospital following an emergency operation for acute intestinal obstruction. Dr Mann had seen his patients the day before, and had planned to leave for the annual meeting of the Maine Medical Association at Rangeley the very day on which his death so suddenly and unfortunately occurred.

Dr Mann was born at Baillie, New Brunswick, Canada, May 18, 1868, the son of Thomas Andrew Mann and Sarah Ann Gilmore. He was a graduate of the College of Physicians and Surgeons of Baltimore in 1892, and of the University of Bishops College

Faculty of Medicine of Montreal in 1900, receiving the degrees of M D and M D, C M, respectively. He first practiced medicine in Monticello, Maine, and then removed to Houlton, where he had practiced for over thirty years. He did postgraduate work at the Boston University during 1919 and 1920. He was a member of the Visiting Staff of the Madigan Memorial Hospital and the Aroostook Hospital, and had acted as lecturer to student nurses at both institutions for several years. Dr Mann was a charter member and ex-President of the Aroostook County Medical Society, a member and ex-President of the Maine Medical Association, a Fellow of the American Medical Association, a member of the British Medical Association, a member of the Council of Physicians and Surgeons of New Brunswick, Canada, and had been a Fellow of the American College of Physicians since April 8, 1929. In addition, Dr Mann was a Director of the Aroostook Anti-Tuberculosis Association, a member of the Houlton School Board (serving his second term—its Chairman during 1931) and a member of many local organizations.

Dr Mann was keenly interested in civic and educational affairs. He was an eager student of medicine, his counsel was often sought. His fund of amusing stories, his ability to quote poetry, his genial personality made him welcome in any group. Above all, he was one of the ablest internists of his state, and a brilliant physician.

DR BYRON FULLER BARKER

Dr BYRON FULLER BARKER (Fellow), Bath, Maine, died on April 29,

1932, from acute appendicitis. Dr Barker was born in Bath, November 19, 1872. He received the degree of Bachelor of Arts from Bowdoin College in 1893, and the degree of Doctor of Medicine from the Jefferson Medical College in Philadelphia in 1896. He was a member of the Medical Staff of the Bath City Hospital, and taught a course in Internal Medicine to the Nurses of that institution.

Dr Barker was an ex-President of the Sagadahoc County Medical Society, ex-Secretary of the Bath Medical Club, a member of the Maine Medical Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1931.

Quoting from the Maine Medical Journal, "His life was devoted to the practice of medicine, he read widely, had few if any, side issues, took short and few vacations and was a model of what a careful, cheerful, conscientious medical advisor should be. He studied the latest medical treatises and had them ready in mind for emergencies. He was keen in diagnosis, was trusted implicitly, and was a pleasing gentleman in the house of sickness."

(Furnished by E. W. GEHRING, M D, F A C P, Governor for Maine.)

DR BENJAMIN FRANKLIN SHUTTLEWORTH

Dr BENJAMIN FRANKLIN SHUTTLEWORTH (Fellow), died at his home in Clarksburg, W. Va., March 31, 1932, from cardiac failure, aged 54 years. Dr Shuttleworth was one of the most prominent physicians of the State. He received his Bachelor of

Arts degree at the West Virginia University before entering Jefferson Medical College of Philadelphia, from which he was graduated in 1905. Since graduation, he practiced in Clarksburg, where he was universally esteemed by the profession. Dr. Shuttleworth was honored by being appointed to the West Virginia State Council of Health. He belonged to the Harrison County Medical Society, and was an ex-Presi-

dent of the West Virginia State Medical Association. He was a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1922. His wife, surviving him, was Miss Rachael Farris.

(Furnished by JOHN N. SIMPSON, M.D., F.A.C.P., Governor for West Virginia.)

The September Number of the Annals of Internal Medicine

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Clinical Aspects of Gastric Secretion

By ARTHUR L. BLOOMFIELD, M D, F A C P,
San Francisco, California

THE study of gastric secretion in man may be approached from either of two standpoints. First, there are the problems dealing with the mechanism of the formation of the various constituents of the gastric juice and with the variations of these constituents under "normal" or "average" conditions. Here we do not seek that utility which is implicit in clinical observations, we deal with a phase of animal (human) physiology. But there is another aspect which is of importance to the pathologist and to the physician, namely, the correlations which may exist between aberrations of secretion and disorders of structure or function of the stomach. This study is practical and empirical and it serves no purpose unless its results aid in diagnosis or lead to useful therapeutic action.

Ideas about the physiology of gastric secretion in man have been based largely on the results of animal studies. The pouch preparations of Pavlov and of Heidenham modified by a host of pupils and followers still represent the usual method of study,

and while occasional observations on men with gastric fistulas such as those of Beaumont and more recently of Carlson have been recorded, most of the human studies have been carried on by clinicians with a view to developing diagnostic methods in disease. Physiologists working in this domain, curiously enough, seem disinclined either to use the human subject or to accept as sound the results of human studies, and a scrutiny of the recent literature suggests that those dealing with men on the one hand, and with dogs on the other, seem destined, like the parallel lines of Euclid, never to meet on common ground. None the less, we believe that by proper methods accurate measurement of the gastric secretions of men can be made and it is the present purpose to summarize the results of such studies both in normal people and in disease.

METHODS

Since the popularization of the stomach pump sixty years ago the gastric juices have been readily accessible for study, but bitter debates have been carried on as to what sort of stimulus is most appropriate for promoting a flow of juice. That it should be some sort of meal which the subject consumes seems to be agreed

Presented at the San Francisco Meeting of the American College of Physicians, April 4, 1932

From the Department of Medicine, Stanford University Medical School

upon by common consent despite the fact that such a procedure defeats its purpose at the start, pure secretions are then unobtainable and one recovers for study gastric juice mixed with a variable and uncertain quantity of foreign substance. Indeed the very essence of the procedure of the animal physiologist—the expedient of the isolated gastric pouch—was designed to evade this difficulty and to allow the collection of uncontaminated secretions. Within recent years pharmacodynamic substances, such as histamine, which powerfully stimulate gastric secretion and which can be administered parenterally have become available so that pure gastric juice can now be obtained from men under standard conditions. But in practice most clinical workers cling with almost sentimental tenacity to the idea that a meal of some sort must be eaten if the stomach is to reveal its true activities. The principal argument has been that histamine is unphysiological and that to test its function one must give the stomach normal work to do—namely, a meal. From the standpoint of the physiologist such a claim is, of course, absurd. One need only to recall that the standard stimulus used in animal physiology—the electric current—is one which the animal in nature does not encounter at all. Furthermore, who is to say what sort of a meal would constitute the normal for any particular person, certainly there is no reason to regard the usual doses of bread, gruel or meat as especially suitable. Rather it would seem important to abandon these anthropomorphic concepts of gastric activity and to invoke the basic principles which must

be fulfilled with any adequate functional test. The matter has been discussed in detail elsewhere,¹ but briefly, it may be said that the stimulus must be a uniform one capable of repetition under approximately identical conditions, that it must impose stress on the function to be tested and that in practice it must yield useful information. The ordinary test meals clearly fail to meet these specifications, they impose no tax which will bring out the maximum secretory capabilities of the stomach, they approach a standard stimulus only very roughly and the variable mixtures of food and gastric juice which are obtained for analysis are unsuitable for quantitative studies. Histamine, on the other hand, has made possible accurate estimations of gastric secretion; it fulfills all the criteria which have been enumerated above. If the drug is given hypodermically, pure gastric juice may be withdrawn from the stomach just as from a Pavlov pouch. The actual technic of the procedure has been amply described² and need not be reiterated here. Suffice it to say that if the total gastric secretions are aspirated by continuous suction after a suitable injection of histamine a constant sequence of events takes place in normal people. For the first few minutes there is no evidence of increased secretion but during the second ten-minute period the volume of juice is definitely increased and during the third or fourth period a maximum flow is attained which then gradually subsides. Coincidentally with increased rate of secretion the titratable acidity rises and reaches a peak, usually after 20 to 30 minutes. The maximum

amount of juice secreted during any one ten-minute period and the highest acidity attained after a standard dose of histamine are values which may be taken as substantial indices of the secretory capability of the stomach in question. If the technic of aspiration is carried out properly, beautiful smooth curves are obtained which reflect the accuracy of the procedure. A few sample curves are shown in figures 1 and 2.

CLINICAL PHYSIOLOGY

The first problem was to work out normal standards to be used as a basis for comparison with the results in disease. Details of such studies have

been reported elsewhere.³ Perhaps the most striking fact which emerged was the wide variation both of acidity and of volume of secretion which existed in a group of healthy people without demonstrable gastric disorder. To be sure, the majority of the values fell in a fairly narrow range but there were sufficient exceptions to make it clear that no rigid standards of normality can be laid down, indeed there are a considerable number of apparently normal individuals who secrete no juice at all but only a little mucus. All that one can do then is to plot distribution curves and to assume that the nearer the values in a test case lie to the mean the more likely they are

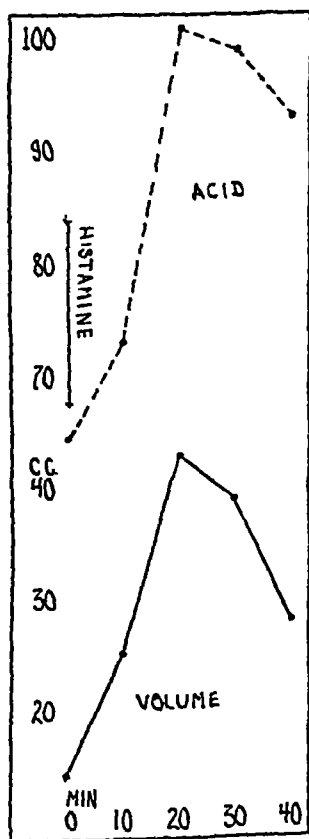


FIG 1

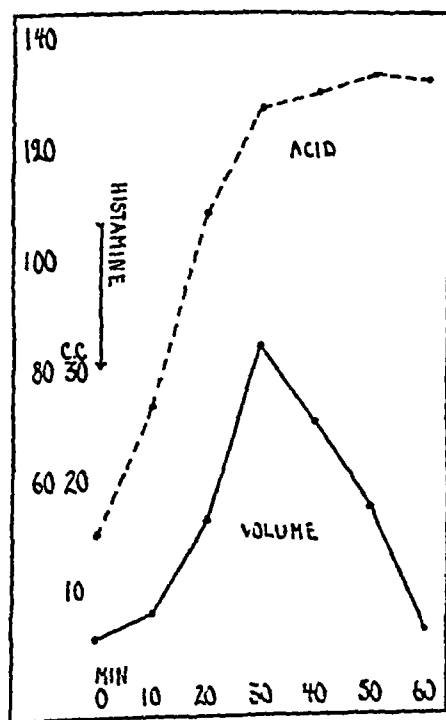


FIG 2

FIGS 1 and 2 Curves showing volume of secretion and acidity at various intervals after histamine stimulation (Bloomfield and Pollard, Jr Am Med Assoc, 1929, xcii, 1508)

to be normal Such distribution curves of acidity and of volume of secretion based on the findings in 100 normal people are shown in figures 3 and 4 It is seen that the largest amount of juice secreted in a ten-minute period fell within the limits of 21 to 35 c c in about one-half of the subjects, but values from 5 c c to 70 c c were encountered So, too, with acid three-fourths of the values lie above 100 but some normals yield much lower figures Other interesting facts are the steady decrease in average volume and acidity with advancing years, and the differences in the sexes which have been pointed out by Vanzant ⁴

These findings in normal people lead to certain reflections as to the physiological significance of gastric secretion, clearly the process is of much less importance to the organism than is, for example, the secretion of urine or the regulation of the acid-base balance Indeed, one may reasonably take the view that gastric digestion in man is a matter of no great conse-

quence and that gastric secretion has failed to develop as a highly standardized process, some mammalian species, such as the rat, even though omnivorous, possess no acid gastric secretion at all (Pollard⁷), and certainly many people though devoid of gastric juice maintain perfect health and nutrition and suffer no digestive symptoms⁸ The breaking down of food is adequately accomplished by the intestinal juices and experimental proof of this mechanism has been obtained by Hines in this clinic This concept is of prime importance to the clinician because, as we shall point out later, if the process of gastric secretion is normally somewhat variable it will clearly be difficult to interpret the findings in disease

BASAL SECRETION

So far we have considered the response of the stomach to a purposeful stimulus But the question of gastric secretion can be viewed from another angle, that of the fasting or basal se-

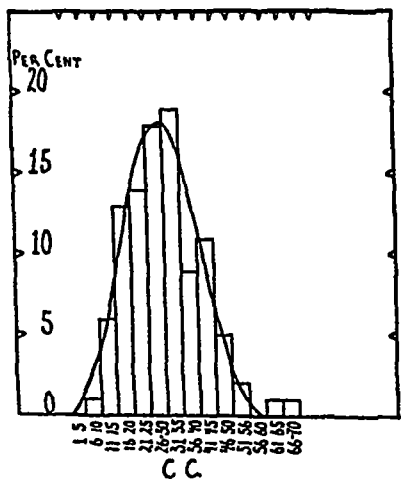


FIG 3

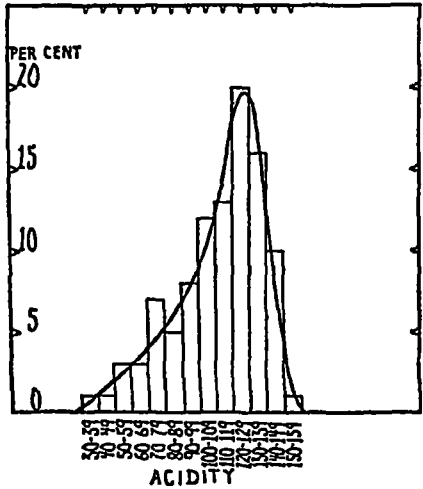


FIG 4

FIG 3 Distribution of highest ten-minute volumes of secretion from one hundred normal people (after histamine) (Pollard and Bloomfield Jr Clin Invest, 1931, ix, 651)
FIG 4 Distribution of highest acidity reached after histamine stimulation by one hundred normal people (Pollard and Bloomfield Jr Clin Invest, 1931, ix, 651)

cretion Even with the subject at rest and without food one must suppose that the secretory mechanism is still under the influence of stimuli whether mediated through the autonomic nerves, or by hormonal or other influences Such is actually the case, and there have recently been recorded systematic observations on the gastric juice produced by people brought as nearly as possible into the "basal" state and disturbed only by the passage of the aspirating tube? Under these conditions it was found that most normal people secrete some gastric juice, it may vary in amount up to 20 or more cc per ten-minute period and the acidity frequently is over 100 (titratable, phenolphthalein) Furthermore, the type of juice obtained from any person is much the same on successive examinations, it is, perhaps, an expression of the activity of his autonomic nervous system When the basal secretion is abundant and highly acid there is but little change after an additional stimulus, even such a potent one as histamine It may turn out that the basal gastric secretion can be correlated not only with other physiological characteristics but with disease as well, but as far as we know adequate studies on this point have not yet been made

PEPSIN

Many attempts have been made to develop clinical methods for measuring pepsin but no very satisfactory procedure has been devised because of the inherent difficulties of ferment titrations Pollard and Bloomfield⁸, using a more accurate modification of previous methods, measured the con-

centration of pepsin and the total output in normal people and in disease Roughly there was a parallelism between the presence of pepsin and the normality of the juice in other respects, that is, whenever acid was abundant there was always an adequate amount of pepsin In some patients with anacidity pepsin was still detectable but in insignificant quantities In no case have we found an abundance of pepsin in the presence of a deficiency of acid or vice versa Measurements of pepsin serve no purpose, therefore, in practical clinical work even though of interest from the standpoint of the physiologist and chemist

CLINICAL APPLICATIONS

We may now turn to the actual clinical uses of measurements of gastric secretion and again it must be emphasized that any conclusions which are reached are essentially empirical It is with the fruits of practical experience and not with theoretical questions that we now have to deal, and it may be said in advance that regardless of method the sum total of information of help in dealing with patients is meager The histamine test has the great advantage of at least yielding accurate data but the application of these data unfortunately is limited Rearrange one hundred pennies as one will, no more than a dollar will emerge It is essential that this be made clear because from time to time articles appear which becloud the real issue insofar as they defend by special pleading, one or another procedure such as the Ewald or the fractional gruel meal and give an errone-

eous impression as to the value of the information to be obtained from any test of gastric secretion

More in detail, the first question which presents itself is whether there is any correlation between the amount and acidity of the gastric juice and the patient's symptoms. This question must be answered in the negative. There is no feature of the patient's complaints which enables one to predict whether his secretion will be scanty or abundant, highly acid or poor in acid. It is true that the type of indigestion which is common in patients with peptic ulcer is often associated with the presence of large amounts of highly acid juice but so many people with identical symptoms have neither ulcer nor high acid that no valid correlation can be made. Furthermore, many individuals with no symptoms at all turn out to have an abundant highly acid secretion or perhaps no secretion at all. The syndrome of "hyperacidity" of the older writers had better, then, be altogether abandoned, especially as recent studies of the mechanism of indigestion show that the symptoms are brought about by motor and not by secretory difficulties.⁹

Turning next from digestive symptoms to anatomical lesions, is there any relation between disease and the type of gastric juice? Under three conditions only have we found a valid correlation. First, in true Addisonian (pernicious) anemia absence of gastric secretion, is, as everyone knows, an almost constant finding. Hence a normal stomach juice weighs heavily against this type of anemia although severe anemias of other varieties (hy-

pochromic) frequently co-exist with gastric anacidity. Secondly, with peptic ulcer, especially duodenal ulcer, both acidity and volume of secretion are usually above the average, and while this is not invariably true it is so frequent that *in a doubtful case* scanty juice of low acidity or absence of acid point strongly away from ulcer as the correct diagnosis. High acid, on the other hand, while *compatible* with ulcer does not make the diagnosis since many normal people have just as high acid values as are found in ulcer cases. With cancer of the stomach one finds just the reverse; anacidity or low acid is present in such a preponderance of the cases that in a doubtful case—say an obstructive lesion of the pylorus—high acid would point away from cancer and towards a benign lesion. Aside from these three specific diseases—pernicious anemia, ulcer and cancer—it must be admitted that in practice studies of gastric secretion have little meaning and as time goes by we find ourselves passing the tube with less and less frequency. As with many other "special tests" in medicine examination of gastric secretion should be done not as a purposeless routine but to answer a definite question and a question which the test is capable of answering. Thousands of gastric analyses—most of them probably inaccurately executed—are done each year without the remotest possibility of serving any useful purpose, whether the acid is high or low or for that matter absent, nothing is usually brought out which either helps with diagnosis or leads to constructive action.

The reader is already thinking of

the many reports on all sorts of diseases—diabetes, hyperthyroidism, arthritis, acne, gall bladder disorders, etc etc,—in which it is claimed that some characteristic aberration of gastric secretion exists. These claims we have been unable to confirm if an adequate technic is followed and if proper controls with due consideration of the age of the patients and other factors are used as a basis for comparison. Distribution curves of acidity and volume of secretion from a large number of miscellaneous cases which demonstrate this fact will be published shortly (Polland).

Finally, a question of interest is whether disease of the stomach leads to alterations of the gastric secretions. Is, for example, a cancer, as it grows associated with progressive diminution in the flow of juice and in its acidity? Hurst¹⁰ and Polland and Bloomfield¹¹ have presented evidence that such is not the case, nor is there any reason to believe that ulcer leads to increased secretion of acid. Rather is it true that

ulcer tends to occur in people who to begin with secrete an abundant highly acid juice just as cancer usually occurs in those who already have a "gastritis" with deficient secretion.

SUMMARY

Because of the wide variations in gastric secretion which are found in healthy people it is difficult to draw conclusions of diagnostic value in patients. This difficulty is enhanced by the crude test meal methods which are usually employed. In practice, measurement of gastric secretion is helpful in the diagnosis of pernicious anemia (and perhaps certain types of hypochromic anemia), of gastric and duodenal ulcer, and of cancer of the stomach. The "routine" employment of test-meals, even in the case of patients with indigestion, is useless, whereas an occasional well conducted measurement of gastric secretion performed to aid in solving a special diagnostic perplexity is sometimes of the greatest value.

REFERENCES

- ¹BLOOMFIELD, A. L., and POLLAND, W. S. The diagnostic value of studies of gastric secretion, *Jr Am Med Assoc*, 1929, xcii, 1508-1513.
- ²POLLAND, W. S., ROBERTS, A. M., and BLOOMFIELD, A. L. The chloride, base and nitrogen content of gastric juice after histamine stimulation, *Jr Clin Invest*, 1928, v, 611-637.
- ³POLLAND, W. S., and BLOOMFIELD, A. L. Normal standards of gastric function, *Jr Clin Invest*, 1931, ix, 651-658.
- ⁴VANZANT, F. R. The normal range of gastric acidity from youth to old age analysis of 3,746 records, *Proc Staff Meet Mayo Clin*, 1931, vi, 297-300.
- ⁵POLLAND, W. S. Personal communication.
- ⁶POLLAND, W. S., and BLOOMFIELD, A. L. Unexplained gastric anacidity, *Arch. Int. Med*, 1931, xlviii, 412-417.
- ⁷POLLAND, W. S., and BLOOMFIELD, A. L. Basal gastric secretion in man, *Bull Johns Hop Hosp*, 1931, xlix, 302-311.
- ⁸POLLAND, W. S., and BLOOMFIELD, A. L. The diagnostic value of determinations of pepsin in gastric juice, *Jr Clin Invest*, 1930, ix, 107-113.
- ⁹For discussion see BLOOMFIELD, A. L., and POLLAND, W. S. Experimental referred pain from gastro-intestinal tract, esophagus, *Jr Clin Invest*, 1931, x, 435-452.
- ¹⁰HURST, A. F. Schorstein lecture on precursors of carcinoma of the stomach, *Lancet*, 1929, ii, 1023-1028.
- ¹¹POLLAND, W. S., and BLOOMFIELD, A. L. Gastric secretion in cancer of the stomach, *Bull Johns Hop Hosp*, 1930, xlii, 307-322.

Standards of Normal in Gastric Secretion

By WALTER C ALVAREZ, M D , F A.C P ,
Rochester, Minnesota

AFTER approximately fifty years of stomach pumping and busy filling of archives with countless papers on gastric analysis, it would seem as if everything worth doing must have been done over and over again. Actually years of search through the enormous literature led me finally to the conclusion that most of the work on standards of normal which should have been done at the beginning has never been done, or at least, has never been done with enough material or with the technic that would satisfy a modern biometrician.

The value of one gastric analysis
For instance. What is the value of one gastric analysis? Through what limits is the acidity of the gastric contents of an individual likely to vary from day to day? Ordinarily when a physician gets a report back from the laboratory he is likely to assume that the figures, 40 free and 60 total, represent data as reliable and unchangeable as those expressing body weight or basal metabolism. But are they so reliable? A search through the literature showed only one paper on the subject and in this the data were so presented that I

could not get the information I wanted.

Accordingly Vanzant and I² studied the secretion of two healthy young women daily for a month. In one, who was fairly phlegmatic, the range of free acidity was from 30 to 46 units and the range of total acidity was from 40 to 66 units. The figures tended to follow a curve which apparently corresponded with the menstrual cycle. In this young woman one gastric analysis would be of some value because the variability was sufficiently small.

The other young woman was more temperamental, and when, during the middle of the month of observation, she suffered a severe disappointment, she became much depressed, and coincidentally, the free acidity rose in a few days from a mean of approximately 36 to a high point of 60 units. It then dropped rapidly to 20, and after a swing back to 46 came to rest again about 36 units. The total acidity followed the same course. Obviously, in this woman a single gastric analysis made during the middle of the month would have been almost without value.

Standards of normal acidity at different ages in men and women
The next question was. What is normal acidity, and how does it vary in the

Read before the American College of Physicians, San Francisco, California, April 4, 1932. From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

two sexes and at different ages? In order to answer this question Vanzant and her associates³ collected data on gastric analysis from 3,746 men and women who were proved to be without organic disease in the digestive tract and otherwise in fair health, and arranged the figures in percentage distribution tables corresponding to five year age groups. Figure 1 shows clearly that gastric acidity rises rapidly during childhood. At puberty the free acid of boys increases faster than does that of girls so that at the age of twenty years the mode or most typical figure for the men is 46 and for the women 31. It is possible that this difference in acidity has something to do with the greater susceptibility of men to ulcer.

The mean and modal acidity of the men falls off with age until finally in the later years of life it coincides with that of the women. The curious feature is that only late in life does the modal or most typical acidity of women fall off, and in them the mean acidity never falls. This makes it seem unlikely that the decline of acidity in men is due to a slow atrophy of the gastric glands because one would expect age to work the same injury to women. Strange to say, Vanzant and her associates³ found a straight line increase in the incidence of achlorhydria (to the ordinary test meal) with age, in both men and women. In men the percentage varied from 0 at the age of twenty-five years to 23 at sixty years, in women the figures were 3 per cent at twenty years and 28 per cent at sixty years. After the age of sixty-five years the percentage fell off gradually, due perhaps to greater longevity of persons with normal gastric acidity.

A study of the percentage distribution curves of total acidities at different ages showed that they were bimodal, in other words, there were two peaks, one representing the group of persons who have free acidity and the other the group who have none. To the biometrician bimodality always suggests the probability that he is dealing with two different varieties of persons. In this case, one type of man has probably inherited a tendency to develop achlorhydria and the other has inherited a tendency to keep his acid throughout life. The difference may be like that which gives to one man even in youth a shiny bald head and to another a musician's mop which lasts into old age. Using the same simile, the gradual falling off of acidity in older men may correspond to the gradual thinning of the hair with age, a thinning which is usually more marked among men than among women.

A study of the range of gastric acidity in apparently normal persons shows that throughout middle life one can hardly speak of a pathologic subacidity unless the free acid titer is below 20 for men and below 10 for women. One can hardly speak of pathologic hyperacidity unless the titer exceeds 75 units for men and 56 for women.

It would seem also that the physician should be slow to alarm patients over the fact that they have gastric anacidity. He should remember that this peculiarity can be found in one of four apparently normal persons aged sixty years. He may with propriety watch the patient with greater care than he otherwise would, but he

need not give expression to gloomy forebodings

The age curve of acidity is shifted bodily by disease Vanzant⁴ has shown that with duodenal ulcer the curves representing mean free acidity in men and women are raised about 12 points but otherwise left unchanged. This is a most interesting point, indicating as it does that these curves represent some biologic peculiarity which is too deeply rooted to be altered with ease.

Now that standards of normal are available I believe that the gastroenterologist should give up the old, cumbersome, arbitrary and inadequate classification of data from gastric analysis into acid, subacid, normal, and hyperacid, and substitute the method used by students of basal metabolism. Only as we physicians come to express acidities in terms of a percentage above or below normal can we obtain accurate knowledge in regard to the influence of different diseases and different types of ulcer in gastric secretion. Work along these lines is now being done on a large scale by Vanzant and her associates. It will be reported later.

Studies in regard to pepsin in health and disease Although much work was done years ago on the amount of pepsin in the gastric juice, it was of doubtful value on account of the crudeness of the technic used. Recent studies with a highly accurate technic⁵ have led us to hope that the estimation of pepsin may give to the clinician information of greater value than that obtainable from a study of the acidity. With the method used, the usual value found in normal persons with a fairly calm temperament is about 90 units,

whereas the range is from 0 to about 500 units. In persons of an active, nervous, and tense temperament the values range up to 2,000 units. In patients with tractable duodenal ulcer the upper limit is about 800 units, and in patients with intractable duodenal ulcer almost all the readings are very high. It is possible, then, that this test will prove to be useful in helping the physician and the surgeon to recognize early those cases of duodenal ulcer in which treatment of any kind is going to be difficult. A study of the acidity alone is not so helpful because there is not enough difference between the values obtained in persons with tractable and in those with intractable ulcer.

Obviously a study of the gastric ferments cannot be of value in the diagnosis of ulcer because persons with a tense nervous temperament or with pseudo-ulcer commonly have as much pepsin as is found in the gastric juice of patients with an actual lesion in stomach or duodenum.

SUMMARY

Data have been published which throw light on the size of the daily variation in gastric acidity and on the reliability of one gastric analysis. In some persons the variation is so large that little value can be attached to figures obtained from one test meal.

A figure has been published which shows the range and central tendency of measurements of gastric acidity for men and women at five yearly intervals from youth to old age.

The mean acidity of men during middle life is about 15 points higher than that of women. The percentage

of persons with an acidity, after an Ewald test meal, increases steadily from youth to old age. The bimodal distribution curves representing total acidity in the various age groups suggest that there are two varieties of the human race: one with a tendency to maintain free acidity in the stomach, and the other with a tendency to lose it. The range of normal variation is so great that it is only an occasional gastric analysis that can be of any diagnostic value.

The curves representing mean free acidity in men and women from youth to old age are raised about twelve points but otherwise are unchanged by ulceration in the duodenum.

Persons with a nervous temperament commonly have pepsin values from fifteen to twenty times the normal. Similar values were found in most of the patients studied with intractable duodenal ulcer. Patients with tractable ulcer had pepsin values usually less than nine times the normal.

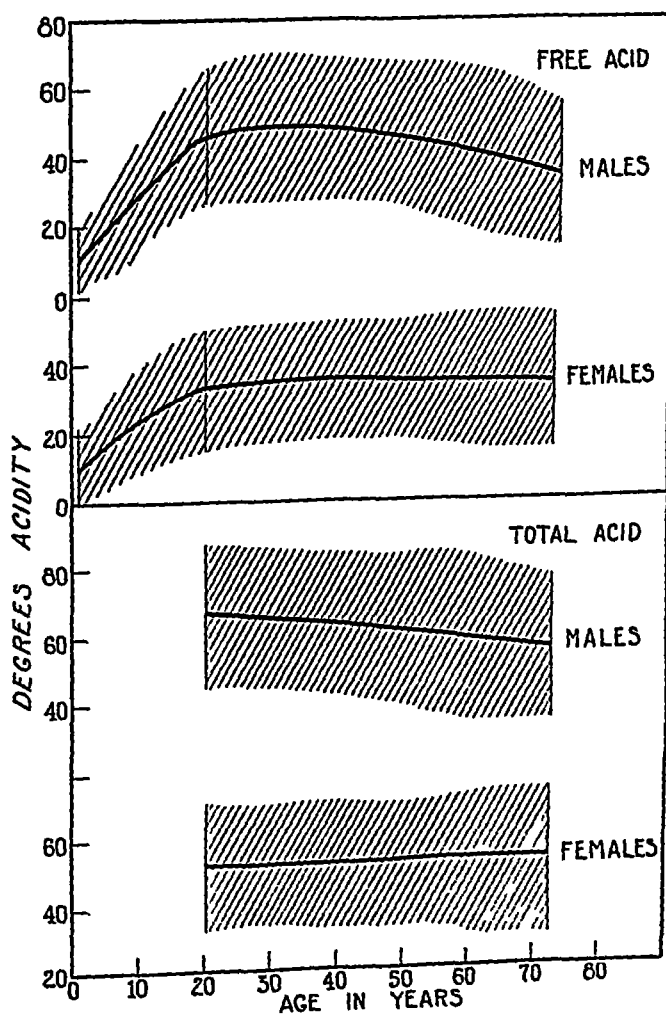


FIG 1 The range (including 80 per cent of the data), and central tendency of free and total gastric acidity in normal men and women by five year age periods from youth to old age

REFERENCES

- ¹OSTERBERG, A E , VANZANT, FRANCES R ,
and ALVAREZ, W C The determination
of pepsin in the gastric content and its
clinical significance in duodenal ulcer
and pseudo-ulcer, Proc Staff Meetings
of Mayo Clinic, 1932, vii, 268-272
- ²VANZANT, FRANCES R, and ALVAREZ, W
C What is the value of one gastric
analysis? A study of the daily varia-
tions in the gastric acidity of two nor-
mal persons, Proc Staff Meetings of
Mayo Clinic, 1931, vi, 419-422
- ³VANZANT, FRANCES R , ALVAREZ, W C ,
EUSTERMAN, G B , DUNN, H L , and
BERKSON, JOSEPH The normal range of
gastric acidity from youth to old age
an analysis of 3,746 records Arch Int
Med , 1932, xlix, 345-359
- ⁴VANZANT FRANCES R Personal communi-
cation to the author

“Medicine” of the American Indian

THE theologico-physical dualism of the American Indian is best illustrated by his use of the word “Medicine” To the person brought up in the European tradition, medicine connotes some chemical, some regime of life or physical procedure used for its actual alternative effect on the body To the Indian the term means much more He may use the word to refer to an herb or drug, but more often it means some supernatural article or agency which may be of aid in curing disease or just as often the same thing may be invoked to insure the success of some individual or tribal undertaking Anything under the sun might achieve such therapeutic or mystical quality, might become “medicine”. Once invoked, the article thus dignified was held to be powerful and sacred It might be an animal, a bit of wood, a finger from a powerful foe, a spear or a pipe But once consecrated, it was never harmed if animal, or never again used for lay purposes if it were a utensil This did not mean that the article was revered in itself as the Indian was always careful to distinguish the fact that its symbolism alone hallowed it These articles or herbs or even formulae which were supposed to have healing or other benign properties were spoken of as “good medicine”, while evil influences or things were referred to as “bad medicine”

From *Medicine Among the American Indians* by ERIC STONE Paul B Hoeber, Inc , 1932. (See review in this issue)

Asthenia: Clinical Types and Principles of Therapy

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IN THESE times of stress with life being lived at an ever increasing pace and with financial burdens, familial cares and a multitude of other distressing factors putting a strain on the physical, mental and emotional powers, the subject of asthenia has become an important one. The term "Asthenia", in common with a number of the other terms current in medical parlance, is not used critically but is applied without discrimination to all types of weakness, debility, depression, constitutional inadequacy, or even nervous instability. It is customary to regard as asthenia, the state of weakness manifested in the course of convalescence of most serious illnesses, but in many cases this is simply a condition of general debilitation in accordance with physiological law which will disappear as the organism with the aid of diet and the proper hygiene is able little by little to recover its muscular and nervous force. Certain of the severe infections and intoxications, however, are definitely "dysthenizing" agents and the patients experience a true, pathological asthenia as a complication of their disease. Emotional

shocks, worry and prolonged nervous strain are also able to produce asthenia.

The basis of all physiological life is the maintenance of a balance between two or more counteracting forces and as a result there is the equilibrium in endocrine function, in the production of epithelial and connective tissue cells, in vasoconstriction and dilation, acidity and alkalinity, in the heat regulation of the body. The two states of asthenia and hypersthenia seem to be but variations of the normally maintained eusthenic state. Asthenia has been rather aptly styled a diminution of "potential". All energy produced by the metabolism is organized and distributed by the nervous system and just as electrical apparatus may be "geared" at high speed or low speed, human beings may experience an habitually increased influx of nervous force into the muscles and brain and be hypersthenic, or the influx may be less than is the portion of the normal individual and they will be classed as hyposthenic or asthenic. Asthenic individuals may have no discoverable functional disorders and no especial worries or cares, yet they fatigue more easily and rapidly than the normal person while the hypersthenic subject

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may be of ordinary stature, development and function and may even show a low arterial tension, yet he is able to accomplish an enormous amount of work without notable fatigue, due to the tremendous amount of dynamic force which he possesses. A certain degree of asthenia and hypersthenia are exhibited in the course of routine existence and there are variations from day to day in the normal person's dynamic state. Usually this variation is confined within narrow limits but when it passes beyond these limits it becomes abnormal and there may result an asthenia so profound as to resemble stupor or an hypersthenia reaching almost to the point of mania.

The changes in the dynamic state from normal to pathological might be classified as follows

Hypomania
Exaltation
Hypersthenia
EUSTHENIA
Hyposthenia
Asthenia
Stupor (?)

Asthenia¹⁻⁴ is a well-defined state in which there is an insufficient influx of nervous force to support either muscular or intellectual effort, and in which the least movement or expenditure of energy provokes an overwhelming fatigue. Rest and sleep do not alter or improve the condition; diet and medications are of no avail. The asthenia includes both striated and smooth muscle fibers and the digestive system is subject to the same abnormal state of easy exhaustion. There may be slowing of respiration due to asthenia of the diaphragm. Londe⁵ finds that there is feebleness of the voice or com-

plete aphony, that the physiognomy becomes dull and the eyeballs sink in the orbits due to insufficiency of the muscle of Muller. There is no dulling or confusion of the mental processes and no loss of perception, although the patient may be unable to read, write, engage in conversation or follow a direct line of thought due to the fatigue which is engendered.

Asthenia is a purely functional state and may even appear without discoverable organic or emotional cause, at autopsy no trace is left on the organism. Benon⁶ states that it is remarkable to note the rapidity and completeness with which the asthenia may develop in a few hours or days, its immobility and invariability for an indefinite period of time, and its disappearance as rapid as its installation. It may last but a half-hour or it may become chronic and permanent, the attacks may last for a few months or for a year or two, then disappear and recur at a later date. Where there has been one prolonged attack of asthenia and the patient has returned to a normal state, it may be assumed that there will be a recurrence. Tastevin⁷ reports three interesting cases of primary, uncomplicated asthenia, in one of which the condition was permanent and in the other two was recurrent with periods of normal health intervening.

I The first case was a young man 33 years of age. He had been a lively, active child but at the age of 14 years, when he was a student at the Sorbonne, he felt himself progressively growing weaker following frequent painful headaches and intellectual overwork. For some time he tried to continue his studies but having reached the age of 21 and finding this state persisting he attempted suicide and was interned in an

institution He left the institution after a time in exactly the same physical state but resigned to his situation When the case was reported some years later, the patient had been in a state of permanent asthenia for 15 years, all his movements were slow and he became fatigued with the least effort He described his malady as a feebleness of the nervous system with headache, inertia, lack of energy and decision It took him two hours to undress himself When he tried to read, his headache augmented and he was obliged to stop It was in bed that he was best His sleep was normal In the beginning when he was a student, he worried over his condition but now he cared for nothing, he had no interests and merely lived from day to day

II A woman, 74 years of age, had been in an institution for eight years following an attempt at suicide in the course of an attack of asthenia At the age of 24 years, being newly married and pregnant, she had had an attack of asthenia lasting nine months, following numerous difficulties with the parents of her husband From that time, there had been recurrences almost every year, lasting about six months and coming on at any period of the year The condition came on almost insensibly and disappeared in about the same manner, within four or five days she found herself ill or cured During the attacks she remained in her chair inert, she did not wish to talk, would have liked to read but after four or five lines could no longer recall what she had read and after commencing several times put aside her book She was tormented by her condition, her one fixed idea was her malady When she was 66 years old, feeling discouraged at having spent her whole life in this way, she tried to jump from a fifth story window, and had been interned in an institution for the eight years following During the last five or six years there had been no recurrences During the attacks, this patient had rachialgia and constipation but despite her age, there was no weakening of her intelligence

III A woman, 49 years of age, 12 years previously had had an attack of asthenia lasting 18 months Several years later, there was another attack, and sometime after that

a third Eighteen months after the third attack, she found herself again in this state and feeling it was better to die, tried to take poison and was interned in an institution She said that at these times she suddenly experienced a powerlessness to act, she wished to do things but had not the force to accomplish what she wished to do Her appetite was good but it was necessary for someone to feed her She remained apparently stupified in her chair, reading fatigued her too much and writing was worse There was a complete lack of ideas and her memory failed her, she responded to questions but liked better not to talk During the attacks there was no headache but stiffness and constipation existed She was well for variable periods of time and then this all recommenced, the asthenia disappeared in a few days

It is notable that in every instance the attempted suicide was not because of any mental aberration but because of anxiety and discouragement over the condition Tastevin states that the patients may be completely unmoved by what goes on about them, good or bad, but they have an excessive tendency to worry about their own incapacity, which will be manifested according to whether the subject is of an equable, irritable, impatient or anxious temperament

There are two forms of asthenia, the severe objective form described above and a light, subjective form in which the individuals are able to mask or overcome the asthenia and engage in business or follow a routine of social activity In the course of general practice in this country up to the present time, asthenia of the objective type has probably been observed most frequently as a complication of various acute disease states

For example in a recently treated case of intercostal neuralgia lasting less than two

weeks, after the pain and other manifestations of the illness had disappeared, the patient found herself in a state of objective asthenia. This extreme weakness was obviously not due to debilitation, the patient and her family believed that she had recovered from her illness yet she was prostrated on the slightest exertion. After an attempt to dress herself or comb her hair, she fell on the bed exhausted and gave up all thought of activity of any sort. The asthenia persisted for about two weeks, then disappeared and the patient returned to her usual routine of household and social duties.

In another case, the patient had acquired a severe streptococcic infection in his hand, with the institution of proper treatment, the infection was controlled fairly promptly but for two or three weeks the least effort provoked an overwhelming fatigue which it was impossible to combat.

The prostration following an attack of gripe is an outstanding example of asthenia. Andrews⁸ in an interesting article on grippal infections pleads for more serious consideration of the extreme weakness and cardiac instability following an apparently trivial attack of gripe. He states that he is often consulted by individuals who have not been well since an attack of gripe as long ago as 10 years yet the patients emphasize that they were not critically ill. The following case reported by Benon⁹ appears to be an instance of the failure to identify post-grippal asthenia, and the consequences which may be expected if the patients are not kept at repose until the regulating neurosthenic mechanism has righted itself.

This was a man, 31 years old, in whom the asthenia had developed at the age of 12 years and had become chronic and incurable. There was no family history of nervous disease. As a child the patient had had no serious disorders and his physical and mental development were normal. When he was

12 years old, he had an acute illness the exact nature of which is not known, he had a severe cold with fever and cough, remained in bed only a few days and no doctor was called. From that time there had been no infection, intoxication, traumatism or emotional shock, but although he was never really ill, he complained of the most diverse maladies and consulted all the physicians in the neighborhood without obtaining any relief. He was incapable of performing any heavy work or of earning his living although his intelligence was normal. He presented symptoms of *general nervous asthenia*, complaining of fatigue, weakness, headache, backache, gastric pains, diarrhea, constipation, loss of memory, insomnia, numbness and buzzing in the ears. He was unable to read because his vision became cloudy after a short time. He stated that he had not been strong since he was 12 years old and had grown without becoming any stronger.

Perhaps the largest group of patients showing a true objective asthenia which has become permanent are those who have never returned to their normal state after having influenza in 1918. These patients are receiving a great deal of attention at the present time both from the medical profession and the pharmaceutical laboratories, but here also the condition is not recognized as asthenia. The subjects are said to be suffering from constitutional inadequacy, functional depletion of the adrenal mechanism, disturbed thyroids, or chronic invalidism of indefinite origin, and their symptoms are listed as lack of strength, loss of initiative, subnormal temperature, low blood pressure, poor circulatory tone, weak action of the heart, weakness of the voluntary muscles, nervous depression, etc.

Rogoff and Stewart¹⁰ in a study of Addison's disease cite seven cases of adrenal cortex deficiency. The seventh

case in this series seems to be a typical case of post-influenzal asthenia

This patient after six months in a state of objective asthenia sought hospital care for the persistent weakness and fatigue. Repeated roentgenographic and laboratory examinations were made. He was given dilute hydrochloric acid, iron and arsenic, suprarenal gland and ephedrine but there was no improvement in the condition. With the administration of cortical substance the patient improved but it is possible that the benefit was derived from the systemic effect of the cortical hormone, the most important function of which is to spur oxidation and further metabolism generally, and not to any direct effect on the asthenia.

Asthenia, then, cannot be confused with states of debilitation since profound asthenia may be noted where there is no debilitation and a state of debilitation may exist with no evidence of asthenia. There are certain factors which are able to produce asthenia and which might be called "dysthenizing agents." Intellectual and physical overwork, pain, disturbing emotions, certain fevers, infections and intoxications such as pulmonary tuberculosis, syphilis, typhoid fever, botulism, or malaria, the important events in the sexual cycle, may all be followed by asthenia of variable intensity. Benon⁶ states that in the case of severe shock or trauma to any part of the body, if at the time of the shock or wound there has been cerebral disturbance with a total loss of consciousness of short or long duration, the patient is liable to a subsequent chronic asthenia. Yet maladies of the brain, itself, are not necessarily accompanied by asthenia and it is not unusual to see a completely shattered nervous system without a trace of asthenia. In tabes neither the ataxia nor the hypotonia

seems to produce asthenia, in Parkinsonism there is asthenia associated with rigidity and hypertonicity. The paralysis which is an almost constant finding in diphtheria has been spoken of as a form of asthenia but here there are definite and well-marked lesions of the spinal cord and peripheral nerves. A natural temporary asthenia is often noted in adolescents during the period of growth.

TABLE I
DYSTHENIZING FACTORS

- 1 *Pain*
- 2 *Overwork*
physical
intellectual
- 3 *Stroke*
- 4 *Total loss of consciousness*
from trauma to head, trunk or members
from shock
- 5 *Strong emotions*
anxiety and worry
familial
financial
vexation
anger
fear
jealousy, love, hate
religious fanaticism
- 6 *Neuropathies*
nervous affections
neuroses
psychoses
migraine
- 7 *The important sex epochs*
probably the chief physiological factor in contrast to the many pathological factors
asthenia may occur during growth
hyposthenic and asthenic children may be transformed after puberty¹¹
diminution or cessation of sexual activity may cause asthenia
menopause
ablation of ovaries
castration
asthenia may be noted immediately after pregnancy¹²

- 8 *Glandular insufficiency or over-activity*
exophthalmic goitre
Addison's disease (?)
- 9 *Intoxications*
coli-bacillosis (?)
alimentary (spoiled meat, poisonous mushrooms, botulism)
gases (CO₂, war gas)
drugs (sublimite, antimonial tartar, etc)
- 10 *Infections (fever in general is accompanied by asthenia)*
influenza and grippé
typhoid fever
puerperal fever
malaria
tuberculosis
syphilis
acute articular rheumatism
exanthematous typhus
cerebro-spinal meningitis
epidemic lethargic encephalitis
uterine infections
dysentery
myocarditis
chronic focal infections
streptococcus infections
- 11 *Certain anemias and malignancies (?)*
- 12 *General disturbances of nutrition (?)*
pancreatic
diabetes
hyper- and hypo-glycemia
hepatic
hepatitis
azotemia
icterus
cholemia
renal
uremia
albuminuria

Asthemia of the subjective type is probably quite common but it may be so vague as to be difficult to distinguish. It may be either constitutional or acquired and like the objective form it may be temporary or chronic. The constitutional asthenic is an individual who does not appear ill; he possesses a certain degree of health but is incapable of augmenting his capital

of energy by exercise, diet or hygiene as a normal person may do. These persons spend their lives guarding against fatigue, they recognize their limitations and avoid crowds, exercises and sports, and fatiguing pleasures. An acquired subjective asthenia is most frequent where there is a *chronic infection* or as a *sequela of infection*. There is the same feeling of fatigue and the inability for sustained physical or mental effort but where the condition is permanent, there is a variability in intensity and the individuals are able to mask the asthenia or overcome it by force of their will. Periods of abnormal fatigue and insomnia may occur in the form of attacks with normal periods intervening.

Asthemics are subject to a particular form of insomnia which sedatives or narcotics can rarely overcome, the patients go to sleep readily at 9 or 10 o'clock in the evening but waken at 1 or 2 and remain awake the rest of the night. Headache and eye symptoms, gastric disturbances and constipation are frequent associated findings.

TABLE II
THE ASTHENIC SYNDROME

- 1 *Muscular asthenia*
prostration and general weakness of both the smooth and striated muscles
inability to maintain a standing position for a very long time or make physical effort of any sort
a feeling of weight or heaviness of the body
repose or sleep does not make the fatigue disappear
loss of weight
- 2 *Intellectual asthenia*
slowing of the intellectual process and inability for prolonged mental effort

difficulty of remembering and associating ideas because of the effort required

at times a sensation of emptiness in the head

the perceptions remain intact even though the asthenia may be so profound that the patient seems to be in a stupor

the patient has a perfect understanding of his state but cannot overcome it

3 *Emotional tendencies*

muscular and intellectual asthenia may exist independent of all emotion

two classes of individuals probably following their constitutional predisposition

a the calm resigned type

b those showing a disposition to "unnerving," irritability, or who feel a constant need to change their location

become sensitive and impressionable, believing that chance remarks or acts are meant to apply to them

show great anxiety over their condition and epigastralgia may follow with a sensation of painful epigastric constriction

4 *Nervous symptoms*

accommodative asthenopia is constant, is increased by work and disappears with repose

headache is very frequent

roaring or buzzing in the ears

dizziness

when head is lowered, when walking or when fatigued

vertigo with a fall is rare if not non-existent

insomnia

is habitual

of a particular type—the patient goes to sleep without difficulty at 9 or 10 but awakens at 1 or 2 and can sleep no more if he does sleep with the aid of drugs, he is troubled with nightmare and is prostrated on awakening may feel a need of sleep during the

day, especially when digestion is going on

rachialgia or lumbago

is frequent and at times severe

when localized in lumbar region, subject often believes he has a kidney affection

is increased by work or effort and eased by rest

5 *Visceral asthenia*

a *Gastric asthenia*

appetite may be good and food

may have natural taste but patient may not have the strength to feed himself

usual alimentation is badly supported

slowness of digestion

post-prandial weight or ballooning

aerophagia is frequent

it may be the gastric symptoms which fix the attention of the patient and cause him to consult the doctor¹

b *Intestinal asthenia*

constipation (may be a week or more between evacuations)

sometimes alternating constipation and diarrhea with mucous stools

c *Cardiac asthenia*

manifested more often by tachycardia than by bradycardia

palpitation especially after eating various disturbances of rhythm

tachycardia is not constant, minor causes, physical or mental, produce an increase in the pulse rate but after 3 or 4 minutes it returns to normal

arterial hypotension is the rule

6 *Genital asthenia is always present*

7 *May be signs of endocrine dysfunction, thyroid adrenal*

8 *Subjects are sensitive to the action of drugs*

only small doses are needed
condition is aggravated frequently by tonics and stimulants

HYPERSTHENIA

When studying the problem of asthenia, it must be borne in mind that for every degree of asthenia there is a corresponding degree of hypersthenia. There are cases in which, after the return to normal from a state of profound asthenia, the patients find themselves going into a directly opposite state of increasing muscular and intellectual hypersthenia, showing that the normal regulating mechanism has been suppressed. When the hypersthenia and asthenia appear in juxtaposition forming one attack, and are recurrent, the condition is spoken of as a "periodic psychosis," or as "periodic dysthenia" if they appear separately with normal periods intervening. Mania is regarded by some as the highest expression of hypersthenia, but Tastevin states that in these conditions of dysthenia, there may be extreme activity of the faculties with incessant need for movement, but there is no incoherence of ideas as in mania.

He cites the case of a woman, 30 years of age, who for two years had had attacks of "anxiety" coming on at variable intervals and lasting from one-half hour to a month or more. In spite of a total absence of emotional ideas or worries of any kind, during the attacks the patient was in the state of one who feared a calamity. It affected her as a weight on the chest which prevented her from breathing and as a constriction of the stomach. She felt impelled to move about, at night she tossed in her bed and if she slept for a while, she had nightmare. The feeling of anxiety left as suddenly as it came, after which the patient felt relieved but soon found herself in a state of complete asthenia. The duration of the asthenia was in proportion to the duration of the attack, with attacks lasting only a few hours, the asthenia was of short duration. After an attack lasting $1\frac{1}{2}$

months, the asthenia lasted 10 days. But, with attacks lasting over 3 weeks, after remaining prostrated for some days, she spent a short time in a normal state and then experienced a period of exaltation. She explained the sensation as a feeling of well-being, of being happy to live, she woke early in the morning and did not want to go to bed at night. She sang, laughed and thought of nothing but going out. The hypersthenia lasted about 5 days and she then returned to a normal state.

This case is classified as one of the psycho-neuroses, but it is interesting because when an individual wakes in the morning filled with the joy of living, he is inclined to attribute the fact to good digestion or to nicely balanced endocrine function. However, if this same feeling of alacrity and pleasure can exist as a pathological condition, one is forced to conclude that his dynamic state is not so well founded physiologically as might be supposed.

CONSTITUTIONAL DEPRESSION

Montassut and Delaville¹⁸ describe as "constitutional depression" a state which is easily recognized as one to which presumably normal individuals are liable, especially those possessing the "artistic temperament." In these subjects there is a daily rhythm of fatigue, the fatigue is original and it is chronic although of variable intensity in the course of existence. The awakening in the morning is difficult, somnolence at this hour is invincible and delays the hour of rising. Muscular activity is almost impossible, mental orientation and verbal expression are difficult, the reactions are pessimistic and there is a feeling of powerlessness and uselessness. With physical exercises or a cold bath the inhibition yields somewhat and as the

morning advances activity becomes easier. Luncheon is generally accompanied by an overpowering tendency to inertia. Toward the end of the afternoon when the normal person is beginning to tire, the fatigue disappears and is replaced by a feeling of animation. This is spoken of as the "5 o'clock cure." The feeling is not one of relief that the day's work is finished, since the same amelioration is noted during periods of vacation and it appears in individuals who do night work. With the "5 o'clock cure" intellectual activity becomes easier and more effective and is accompanied by a feeling of well-being and muscular agility. Dinner brings a temporary feeling of fatigue but this is more easily overcome. It is after dinner and often late into the night that he works with all his ability and with a slight intellectual excitation. The constitutionally depressed subject retires late and usually less fatigued and more optimistic than when he awoke. He realizes perfectly what his sensations will be after an intervening period of inactivity and the routine of fatigue and depression that he must undergo on awakening. This paradox of fatigue appears rather scandalous and the individuals get very little sympathy from their family and associates. One surmises that the old saying,

"When the sun has gone to rest,
The lazy man works the best,"

was inspired by the constitutionally depressed

Warm baths, remaining in an overheated atmosphere, profound sleep, the lounging to which they are prone, and the probable change in body chemistry following the ingestion of food,

all aggravate the asthenia. Yet, although it seems necessary to contract a certain amount of physiologic fatigue in order to mask or neutralize the static and essential fatigue, work or effort cannot be pushed beyond a certain limit without producing a state of exhaustion.

NEURASTHENIA

The most important of "the asthenias" is neurasthenia, or nervous exhaustion. Benon¹⁴ believes that true neurasthenia has a special origin and evolution which distinguishes it from all the other asthenic states, and that this is solely the condition of general nervous exhaustion produced by muscular or intellectual overwork. Overwork is defined as a series of repeated and inadequately repaired fatigues which in time will produce a definite syndrome of the asthenic order. Beard,¹⁵ in 1868, was the first to isolate the condition of nervous exhaustion from the vast collection of neuropathic states and to give to the syndrome the name of neurasthenia. He found that most intellectual families possessed one or more neurasthenic members and that the condition was common among business and professional men, among women struggling to maintain a prominent position in society and among people of all types undergoing prolonged worry or nervous strain. But Beard observed that sunstroke might produce this same state of nervous exhaustion. It is true also that while such diseases as typhoid fever may be followed or complicated by a temporary, objective asthenia, after a very severe case of typhoid fever just as after a severe

surgical operation or a serious obstetrical case, the patient may never be able to recover from the nervous exhaustion but will spend the rest of his days in a state of neurasthenia with the easy fatigability, the various subjective mental and nervous symptoms and the sudden and unexpected giving away of his strength. After a close observation of a large number of cases, Beard listed the symptoms as follows, stressing that no symptom was constant and that only a few or almost all might be found in individual cases:

TABLE III
SYMPTOMS OF NEURASTHENIA

The symptoms may be divided into 3 groups, general symptoms, those which are evidences of cerebral exhaustion (cerebras-thenia) and those which are evidences of exhaustion or irritation of the spinal cord (myelasthenia)

I General Symptoms

1 *A feeling of profound exhaustion*

neurasthenics must keep to an ordinary routine as they become quickly wearied with attempting anything new

the treacherousness of nervous exhaustion is one of its most constant characteristics, in the morning subject may be able to work, walk or study but suddenly and from no traceable cause all strength may leave

2 *Deficient mental control*

inability to concentrate

lack of will, courage and self reliance

tendency to worry and fret over trifles

subject to attacks of mental depression lasting but a short time or for a day or more

may be a feeling of hopelessness even in the early and mild stages

wrong word slips in ahead of the one intended

subject to morbid fears

patient may be well aware of his weakness but cannot free himself from these

may have fear of storms, of going in any one direction, of traveling, of open places or of close and narrow places, a dread of society, of being alone, of responsibility, a dread of being afraid, fear of disease (hypochondria), of dust (will not sit down until chair is well dusted and may get up in the night and dust his clothes)

3 *Insomnia*

patient may have no difficulty in going to sleep on retiring but soon wakes and remains awake

may be hours before falling asleep, then sleep the rest of the night

may sleep fitfully with unpleasant dreams and a painfully active mind

may sleep only at night and never by day no matter how wearied

may sleep during the day though especially wishing to keep awake and stay awake all night

may be subject to drowsiness which does not come to actual sleep, dull, heavy, sleepy without the ability to go to sleep

in extremely rare cases, sleep may be normal

4 *Sick headache*

5 *Frequent blushing*

a common effect of nervous exhaustion

from the slightest physical or mental cause

may last months or years and disappear as suddenly as it began

6 *Localized peripheral numbness and hyperesthesia*

7 *Difficulty of swallowing*

8 *Hemi-neurasthema* (may affect one side of the body more than the other)

9 *Rapid decay and irregularities of the teeth*

10 *Tremulous and variable pulse and pal-
itation of the heart (irritable
cart)*

rate and quality vary during
counting
in exceptional cases, pulse is very
slow (40 or less)
there may be alterations in pulse
rate between very high and very
low
cardiac action is powerfully affected
by the mind and under the influ-
ence of the emotions
pulse is frequently compressible

11 *Nervous dyspepsia*

is most commonly found with the
nervous diathesis and may be the
forerunner of a long list of ner-
vous symptoms through all the or-
gans, the eyes, ears, brain, spine
and reproductive system
nervous dyspepsia may take the
place of many other symptoms,
being better when they are worse
and worse when they are better
is relieved by remedies with a seda-
tive and tonic effect such as bro-
mides or electricity, without specific
reference to the stomach
patients have the greatest distress
when the stomach is empty and
even overeating is a relief
mental or physical labor on an empty
stomach may cause pain in the
eyes, head, stomach or general ner-
vous distress all over the body
patients may go for some time on
unregulated diet but suddenly ordi-
nary food will cause distress, flatu-
lence, nausea, diarrhea

12 *Special idiosyncrasies in regard to
food, medicine and external irri-
tants*

patients desire stimulants and nar-
cotics for relief of the exhaustion
but one sign of the neurasthenia is
the inability to bear even those
to which the patients are accus-
tomed (tobacco, coffee, tea, alco-
hol)
some who ordinarily can stand only
small amounts of alcohol when de-
pressed can drink quantities

may have an idiosyncrasy for hot or
cold water

opium is apt to aggravate insomnia

II *Symptoms of Cerebrasthenia* (indicate
that the exhaustion is chiefly cere-
bral)

Tenderness of the scalp

Tenderness of the teeth with whitish
appearance of the gums

Yawning

Disorders of the special senses

changes in "expression" of the eyes
pain and aching in the ears due to
hyperesthesia of auditory nerve
subjective odors and tastes (phos-
phorus or ozone, bitter and sour)
atonic voice (resembles that of
deaf person but can be distin-
guished)

Deficient thirst and capacity for as-
similating fluids

Congestion of the conjunctiva (neur-
asthenic asthenopia or irritable
eye)

the effect of nervous irritation, and
comes and goes under exciting
causes

resembles cold in the eye or the
congestion from drinking

bad in the morning but disappears
at night

*In cerebrasthenia muscular exercise
can be well borne and is frequently
desired and sought*

III *Symptoms of Myelasthenia* (indicate
that the spinal cord is chiefly af-
fected)

Tenderness and pain in any part of
the spine from nape of the neck to
the tip of the coccyx

Creeping chills up and down spine

Convulsive movements of the arm
leg or whole body especially on
falling to sleep

Fidgetiness

one of the myriad results of spinal
irritation

hand and arm may be so "nervous"
patient cannot continue writing
when legs are affected he must
get up and walk even though ex-
ertion aggravates the asthenia

Dilated pupils

there may be sudden and frequent alterations, or temporary inequalities with one contracted and one dilated

One or both ears, hands or feet may be cold to touch even in warm weather, in a hot room, or when thickly wrapped

Heaviness and stiffness of the muscles

Fleeting neuralgias and shooting pains simulating those of ataxy but probably milder

Vague aching in the loins and limbs simulating rheumatism which may follow over-exertion or come on without apparent cause

Pain in the feet

burning and tenderness at the bottoms of the feet

may be only painful spots

in both neurasthenia and ataxia it comes from the spinal cord but in the latter organic, and in the former functional, disease is signified

in some cases may be reflected from the stomach and genital apparatus

Physical exertion requiring either the upper or lower limbs, especially walking and standing, cannot be borne and if persisted in may aggravate the condition

Symptoms showing exhaustion of the upper part of the spinal cord
pain and heaviness in the back of the head

muscae volitantes or floating specks before the eyes

clamminess of the extremities

general or local itching with no change in appearance of the skin

Neurasthenic patients complain that they have "so many symptoms" but the varying and multitudinous symptoms are largely the result of reflex irritations transmitted not only through the ordinary motor and sensory nerves, but also through the sympathetic system and vasomotor nerves. For this reason neurasthenia must be differentiated from the organic disease which it simulates

in many instances, although usually the symptoms of organic disease are fixed and stable while those of neurasthenia appear, disappear and reappear without clear cause

Ballet¹⁰ states that whatever be the clinical form which neurasthenia assumes, a peculiar mental state always accompanies it. The patient is subject to hypochondria and is haunted with thoughts of cancer of the stomach, softening of the brain, disease of the spinal cord or heart disease, according to the location of his distress. His memory fails him, he is disturbed at the sight of a stranger among his usual associates, is timid, fearful, impressionable and pessimistic. However, the neurasthenic is usually quiet, introspective and retires into himself, he does not show the irritability and egotism which is characteristic of the neurotic. Because of the morbid and introspective state of mind and the complicated reflex action throughout the entire body, innumerable "vicious circles" are established with psychic and physical disorders acting and reacting one on the other.¹⁷ The subjects may be fat, hearty and even vigorous looking men who deplore the complete change which has taken place in their personality, the fears and obsessions, the digestive and circulatory derangements, the weakness of will and overwhelming lassitude which all unite to give them a feeling of impotence (Ballet). Beard reports the case of a clergyman of middle age who had suffered from neurasthenia for many years following heat prostration. Among numerous other symptoms were attacks of depression lasting about a day and brought on by any exhausting or disturbing influence. The attacks were usually ushered in

by a feeling of mental exaltation, followed by diplopia and a regular series of minor nervous phenomena

The asthenia of neurasthenia is usually subjective and often presents the peculiarity of localizing in a certain muscular group. Where there is spinal exhaustion and the asthenia is confined to the lower extremities, the patients, usually neurasthenic women, finding they are unable to walk or even to stand believe they are paralyzed and refuse to leave their bed or couch. These individuals may unnecessarily remain helpless invalids for the rest of their lives. Only about 50 per cent of the cases of neurasthenia are cured.

With reference to a constitutional neurasthenia, Ballet believes that where there is an inherited nervous weakness of infectious or other origin, or a neuro-arthritis constitution, the subjects are on the verge of neurasthenia from birth since their nervous system tires even in the course of a regular and quiet life. Londe finds that in such cases there is a failure to adapt the psychic to the somatic life, or a failure to adapt the individual to the exterior world, to his social milieu, to his occupations. However, cases of true neurasthenia among this group of subjects are probably rare.

PSYCHASTHENIA

Often, after the development of a well-marked neurasthenia, new and more serious troubles of a psychopathic order will manifest themselves. Aschaffenberg¹⁸ finds that the stronger the body, the more clearly the clinical picture of neurasthenia will appear, and the more serious and continuous

the damaging influences the more severe will be the exhaustion of the forces, but, even so, in such cases the neurasthenia does not progress beyond itself and the organism remains free from the many and varied psychopathic complications which may develop in a weaker subject or where the nervous diathesis predominates. In such cases, neurasthenia may be but the forerunner of insanity, in the form of melancholia. Hysteria is rare although some hysterical symptoms may be present. Benon lists the possible psychic sequelae of neurasthenia as follows:

- A disposition to anger, unnerving and irritability
- Mental confusion (confusion, usually transitory, in perceptions with no recognition of persons, places or things)
- The obsession phobias
- Alcoholism
- Amnesia
- Hypochondria
- Periodic psychosis
- Mania
- Various forms of delirium (persecution, etc.)
- Melancholia
- Dementia praecox (in young subjects)

Aschaffenberg defines the psychasthenic states as the *slight* forms of psychic disorder which belong to the borderland between mental health and disease, the patients are neither insane nor quite sane¹⁹⁻²³. Janet²⁴ has collected and grouped under the heading of psychasthenia all the functional psychological states, the absurd fixed ideas, the useless and ridiculous manias and unjustified fears and obsessions, which appear and disappear in the form of attacks or crises with

more or less normal periods intervening Janet believes that such mental troubles have a relationship to the regularity of intracephalic pressure and vasomotor troubles, to digestive disorders from gastrointestinal atony, to urinary hypoacidity, cardiac weakness and vascular hypotension, to troubles of the secretions and of genital function

Burr²⁵ considered that the term "psychasthenia" should be reserved for the state of pure mental exhaustion from intellectual overwork and excessive nervous strain (cerebrasthenia) and that neurasthenia is the more or less constitutional state described above by Ballet and Londe

NEUROCIRCULATORY ASTHENIA

The condition variously known as neurocirculatory asthenia,²⁶⁻²⁸ neurocirculatory myasthenia,²⁹ effort syndrome,³⁰ irritable heart,³¹ soldier's heart, disordered action of the heart,³² etc., has been brought to the attention of the medical profession during the different wars in this country and in Europe when the excitement, fear and emotional strain of examination for the army or the exertion of actual service have made active an often latent instability or weakness, which is evidenced principally by disordered heart action. The heart, itself, shows no lesion either of the muscle or of the valves, and patients with true heart disease do not present the syndrome. The symptoms of neurocirculatory asthenia may be listed as follows, stressing again that the symptoms vary in prominence and are not all present in the same individual:

TABLE IV

SYMPTOMS OF NEUROCIRCULATORY ASTHENIA

- 1 Easy fatigue and lassitude
 - 2 Disordered heart action
 - tachycardia
 - forcible beating
 - palpitation
 - arrhythmias
 - systolic apical murmur in 85 per cent
 - 3 High systolic pressure
 - after exercise the systolic pressure rises and the diastolic pressure may drop to zero (Robey and Boas)
 - 4 Left chest pain and soreness of the skin over the left chest
 - 5 Defective capillary circulation
 - 6 Cyanosis of the hands and lips
 - 7 Breathlessness on exertion
 - may be due to
 - (a) reduced vital capacity of the lungs
 - (b) irritable nervous system
 - (c) acid reaction of the blood
- With the addition of only small quantities of CO₂ or lactic acid produced by exertion, the blood due to a deficiency of certain blood constituents becomes more acid than normal and this is immediately signaled by breathlessness, the respiratory center being extraordinarily sensitive to the blood reaction (Lewis)
- 8 Giddiness, dizziness on lowering the head, or vertigo
 - 9 Fainting with or without loss of consciousness
 - 10 Sweating
 - It is common to see these patients shaking with cold and perspiring profusely from the armpits
 - 11 Increased susceptibility to cold and changes in the weather
 - 12 Exaggerated reflexes
 - 13 Tremor
 - 14 Headache
 - 15 Blushing and pallor
 - 16 Irritability of temper
 - 17 Inability to fix attention
 - 18 Sleeplessness or disturbed sleep with bad dreams
 - 19 Aphony

Examination of these patients has shown that in at least 50 per cent there is physical weakness and an inherent nervous instability, for which there is no cure, in the army they are classed as a group of "substandard" men and in civil life they represent the various constitutionally inferior individuals usually with family histories of neurotic and psychopathic disorders. Where the condition was not constitutional, it was found to be due to the too-severe drilling and the hardships of army life, or to be of infectious origin. Many of the subjects showed evidences of a low-grade infection from diseased tonsils and teeth, intestinal infections, incipient or healing tuberculosis, etc., or the symptoms might have dated from an acute infection such as rheumatism, typhoid, dysentery, pneumonia, malaria. Where the condition was attributed to the *rigors of war and army life, no definite constitutional weakness could be determined* but the individuals had been recruited from clerks and office workers, students, waiters, etc., and could not adapt themselves to the new environment.

Lewis explains that when a healthy man takes sufficiently strenuous and prolonged exercise, he experiences a certain well-defined set of symptoms, such as breathlessness increasing in intensity, consciousness of the heart action with elevation of the pulse rate, giddiness or faintness, fatigue, aching over the precordial region and later more violent and widespread pain, and finally exhaustion, and the only difference between this physiological state and the condition known as neurocirculatory asthenia is merely that in

the latter a much smaller amount of effort is required to produce the syndrome.

It would be our opinion that here there is no trace of asthenia but rather an extreme instability of the sympathetic nervous system. Rothschild emphasizes that neurocirculatory asthenia cannot be regarded as a disease entity and that "the name is purely descriptive of the major symptoms, which are referable to the nervous and circulatory systems and associated with an increased susceptibility to fatigue." Crile³³ in a recent paper states that in making a diagnosis, all the cases of mental or psychic origin and all those in which there is infection or a heart lesion should be ruled out, and then if, in the absence of all these, there is extreme cardiac instability, if the pupils dilate as the result of pressure on the epigastrium, if tremors, sweating and cold hands and feet are present, a diagnosis of neurocirculatory asthenia may safely be made. He believes this is a pathological state in which there is an excessive stimulation of the adrenal-sympathetic system and advocates denervation of the glands as a remedy. Simici, Popesco and Sandulesco³⁴ concluded that in many of the cases of permanent cardiac instability there is a latent hyperthyroidism.

HYPOSTHENIA

Mercier³⁵ describes hyposthenia as a state intermediary between "normal" and a complete, well-characterized asthenia. The "hyposthenics" are the patients who are always in a state of hypovitality, who fatigue easily and rapidly, who have no courage, no interests, no amusements. Their diges-

tion is poor, they sleep badly. On examination, no determining affection can be found but they show muscular hypotony and visceroptosis, hypocombustion with a decreased basal metabolic rate, hypothermia and arterial hypotension. The hyposthenic syndrome might be described as general hypofunction, the organism is regulated at a point "between physiology and pathology" and it is difficult to decide where the deficiency commences.

Very often these individuals are tall and spare with sagging abdominal viscera, low resistance and a caliber of mind which makes them unacceptable as companions, and it is this type which is usually thought of as the "hyposthenic habitus". However, there are many tall, spare persons with elongated and ptotic viscera who have good digestion, a healthy mental outlook, emotional stability and a fund of nervous energy beyond the normal. Also, Ballet describes a "precocious neurasthenia", which makes its appearance at puberty or a little later, and is found in patients who are notably taller than the average and whose girth of chest and volume of muscles are not proportionate to their height. These *neurasthenics* are almost always of the male sex, they are long and lean, and their nervous system is endowed with excessive fragility and yields to the slightest shock.

This exaggerated growth of the long bones at puberty is one of the most pronounced manifestations of thyroid over-activity and since a fairly large percentage of these patients show signs of thyroid dysfunction, it is a question whether some are not suffering from hyperthyroidism rather than from either asthenia or any fundamental nervous trouble. In normal in-

dividuals of the same body type, it might be supposed that the thyroid had quickly returned to normal function.

The two terms, hyposthenia and neurasthenia, have come to have a very broad meaning and are used to describe almost any kind of constitutionally inadequate or neurotic individuals³⁰⁻³⁹. There is a nondescript group of patients who are passed around from physician to physician and on to surgeons and various specialists. By the time they are finished, they have had their appendices and gallbladders removed, have had a partial or total thyroidectomy, have probably been to a sanatorium for treatment of tuberculosis or have had treatment for peptic ulcer. No therapeutic measure seems to be of avail and the patients after years of treatment are classed as either hyposthenics or neurasthenics, depending upon the mental attitude, and, one hopes, are given a logical treatment of support and encouragement. Every clinic has its quota of these cases and the physician does well if he can avoid adding to the patient's distress.

It seems that most of these patients are not necessarily asthenic or neurasthenic but are what Kerley speaks of as "50 and 75 per cent individuals"; they are never able to adapt themselves to their environment and are never equal to what is required of a normal person. The histories in these cases show, for instance, that the father died at 47 of pulmonary tuberculosis, the mother died at 60 of Bright's disease and four sisters and brothers died in infancy. Deschamps remarks that every infant is born with a certain amount of "initial force" which remains the distinctive mark of the individual, it is

his biological destiny. It is probably because the terms hyposthenia and neurasthenia are used so indiscriminately that the real condition of asthenia is so little recognized.

ETIOLOGY

Deschamps⁴⁰ states that the sthenogenic function comprehends two principal factors. The production and the distribution of energy. Energy is furnished by the metabolism and the secretions, and the nervous system has the function of organizing the use of the force created by favoring or inhibiting its distribution. The fact that, on the basis of exactly the same physiological state, voluntary and involuntary movements and ideation may vary in rapidity, force and duration, would seem to imply a variability in the transmission of energy. The degree of asthenia or hypersthenia might be referred to as the neurosthenic state, in contrast to the state of physical strength depending upon size and development, nutrition, hygiene, etc. Tastevin says that the organism is dependent upon this neurosthenic function for the power to execute any voluntary movement or for the power to think. The will, the perceptions and the special senses remain intact, but the asthenic lacks the actual power to think or to act so there must be an inhibition somewhere between the ideation and the transmission of the nervous influx which is necessary for the production of muscular contractions or to assemble ideas. In hypersthenia the influx is excessive, ideation is quick and lively with a facility of expression, the individual has a feeling of confidence and self reliance, also, there is a desire for muscular ac-

tivity and all movements are executed with ease and rapidity. Since the nerve centers are the accumulators, transformers and distributors of all energy produced by the unceasing process of metabolism, it follows that in asthenia it is the nerve centers which are deficient.

It has been suggested that anything which precipitates a disturbance of sympathetic function will cause asthenia. The sympathetic system is responsible for automatic or involuntary movements, it is the system which innervates the smooth muscles and the glands. Cannon^{41, 42} states that the neurone relations seem devised for widespread diffusion of nervous impulses, the extensiveness of the distribution of the fibers is one of the most prominent characteristics of the sympathetic, in contrast to the parasympathetic, division of the vegetative system. Also, the connection of single preganglionic fibers with numerous outlying neurones does not seem to be arranged for specific effects in this or that particular region. The sympathetic is in close relation with the cardiovascular, the digestive, and genito-urinary systems. The muscles of respiration are striated muscles and have no connection with the sympathetic but those surrounding the bronchioles are smooth and are subject to vegetative control. The fibers concerned in the maintenance of arterial pressure, the heart rate, the size of the pupil, etc. are constantly discharging while others such as those leading to the sweat glands are normally at rest, all parts are capable of reflex excitation and inhibition (Bard).

The results of excitation of the two divisions of the vegetative system might be listed as follows:

TABLE V

VAGOTONIA	SYMPATHETICOTONIA
myosis and ciliary contraction	dilation of the pupils
increased secretion of saliva	exophthalmia
contraction of bronchioles	dilation of bronchioles
bradycardia	tachycardia
hyper- and at times retro-peristalsis	inhibition of peristaltic movements
gastric hypermotility and hypersecretion	inhibition of gastric secretion
vomiting	relaxation of stomach and intestines
constipation	diarrhea
bladder evacuation	bladder retention
	<i>extreme weakness</i>
	tremors in the skeletal muscles
	syncope
	"goose-flesh"
	erection of hair
	hyperhidrosis
	from forehead
	from axilla
	from palms and plantar surfaces
	constriction of the arteries
	pallor
	cold extremities
	various ischemias
	liberation of sugar from the liver
may be sequence of acidosis, elevation of vagal tonus and vaso-dilation	may be sequence of alkalosis, elevation of sympathetic tonus and vaso-constriction
high blood potassium	high blood calcium
high blood phosphorus	low blood phosphorus
vagotonia increased by pilocarpine	sympathicotonia increased by adrenalin
vagotonia decreased by atropine	

When the sympathetic division of the vegetative system is unduly excited, a definite set of symptoms will be produced, chief among which are *weakness* with a loss of the feeling of stability and possibly tremulousness, tachycardia, sweating, diarrhea, and vascular contractions causing pallor or localized ischemias

In the nervous hierarchy, the sympathetic is regarded as the connecting link by which cerebral activities act on the viscera. Bard⁴³ believes that the marked tendency of the sympathetic to react vigorously and as a whole under conditions of stress implies control of the system by a central mechanism. Also, all sympathetic discharges can be broken by central inhibition or augmented by central excitation.

The vasomotor center is situated in

the bulb. Bard states it is certain that a narrowly localized bulbar mechanism makes a definite connection with the sympathetic outflow to the arterioles. Experimental work indicates that there is a single cardiac center in the bulb, controlling and coordinating vagal and sympathetic discharges to the heart. The vasoconstrictor, vasodilator, cardioaccelerator, and cardioinhibitory mechanisms are closely related physiologically and anatomically they appear

to be closely juxtaposed in the medulla oblongata. Deschamps states that the bulb has been proven to be the most sensitive and easily affected of the nervous centers and that asthenia is especially a bulbar state. In asthenia and in neurasthenia, there may be constant alternating of vascular contraction and dilation and extreme instability of the pulse with variations of cardiac rhythm merely on moving. A low blood pressure is a constant finding in asthenia but it is also common in hypersthenia. We have observed one of the most truly hypersthenic normal individuals that could be found whose systolic pressure during the most active period of his career was consistently around 100.

Bard finds, however, that there is no indication of a localized bulbar center for such sympathetic processes as the secretion of sweat, the erection of hair, inhibition of gastrointestinal motility and dilation of the pupils.

In the organization of the central nervous system, each of the lower mechanisms is influenced or controlled from above, the higher levels may not be necessary for their function but they are able to influence it. Superimposed on the bulbospinal mechanisms controlling the sympathetic is a mechanism located at the base of the diencephalon which is capable of causing a simultaneous discharge over the entire sympathetic system and which is activated in times of stress and emergency (Bard). Huber and Crosby⁴⁴ state that the diencephalon is a primary center involved in various types of emotional expression. The diencephalon is divided into the hypothalamus, the epithalamus, and the dorsal

and ventral thalamus. Various researches indicate that the thalamus is closely linked with the whole range of pleasurable and painful qualities, irritation or injury of the region may change the whole affective attitude of a person. Pain apparently comes into consciousness in the thalamus. The diencephalon also appears to contain the neural mechanism essential for the maintenance of body temperature and it is significant that exposure to cold and strong emotional excitement call forth similar bodily changes by activation of the sympathetic through stimulation of the diencephalon. Pain and disturbing emotions are two of the most important of the dysthenizing factors. Also hypothermia and increased susceptibility to cold are common findings in asthenia and changes in the affective attitude of the subjects are frequent. There is much to suggest that it may be in the diencephalon that the mechanism regulating the neurosthenic function is situated.

Londe finds that among maladies of the nervous system it is those of the cerebellum which are most often accompanied by asthenia and he believes that asthenia is a cerebellar-sympathetic phenomenon.

Danielopolu⁴⁵, after 20 years' research, states that the vegetative system possesses an automatic tone which is maintained by the action of the electrolytes, the secretions and the various substances produced by the vegetative organs themselves. Normally these are furnished in such proportions that there results an ideal milieu for the maintenance of functional equilibrium with the two physiologically antagonistic groups, the sympathetic and para-

sympathetic, in a state of permanent and equal excitation. But over the whole system reign the encephalic coordinating centers and the cerebral cortex, which has an incontestable influence on the organs with vegetative innervation. The cardinal factor in asthenia is the actual inhibition of nervous influx necessary for voluntary movements and for the process of thought, in hypersthenia the ease and rapidity of all voluntary movements and the quick ideation are the predominant characteristics. It might be logical to suppose, therefore, that the dynamic state is controlled at the highest level with various reflex influences on the lower mechanisms, but the reflex action between the different regions is so strong that it is difficult to determine just where the inhibition occurs.

Regarding the constitutional states, Pende⁴⁶, Garrod⁴⁷, Draper⁴⁸, *et al*, like to speak of asthenic, hyposthenic and hypersthenic types which seem to have reference mostly to the endocrine glands and to embryonic development. The asthenic type is supposed to result from such factors as an overdeveloped lymph system, too much stroma for the parenchyma, or defects in the chromosomes; Deschamps believes that what is transmitted is a defective structure of the protoplasm and a certain physicochemical aptitude. However, there are all sorts of constitutional deficiencies and it would seem that a condition could be regarded as constitutional asthenia only when the deficiency is in the nerve center responsible for regulating the neurosthenic state. Londe states that when the asthenia is constitutional it may mani-

fest itself from birth in the slowness and rarity of the child's movements, the difficulty even of swallowing and in the cry. Since clinical study fails to associate the asthenia with any cause whatever, it must be congenital.

DIFFERENTIAL DIAGNOSIS

The condition of asthenia is to be distinguished from such states as atony, apathy, lethargy or melancholia.

Asthenia is a *dynamic* state, atony, or the abolition of muscular tone, is a *static* state of the muscles. The sthenia or dynamism is the active phenomenon of the sthenogenic function and the tonus is the passive or automatic phenomenon. Muscular tone, which is not the same as the reflex, is a state of automatic contractility, a state of tension (Deschamps). There may be atony due to lack of exercise, to stretching and sagging of the visceral ligaments and muscles with a consequent elongation and ptosis of the organs, or after pregnancy with the relaxation and loss of tone of the entire abdominal musculature. This state of atony, however, need not be accompanied by any degree of asthenia.

Tastevin explains that apathy is a state of *activity* which is generally constitutional and in some respects resembles asthenia. When the apathetics speak, their voice is slow and relatively low; their gestures are slow. Their motive reactions of emotional origin are restrained; where a normal person will laugh, the apathetic will smile. Apathy differs from asthenia in the fundamental respect that while the asthenic is rapidly exhausted when he moves, the apathetic can accomplish as intense and as prolonged move-

ments as a normal person. On the one hand, it is a question of the supply of nervous matter, and the influx is soon exhausted, on the other hand, because of a constitutional nervous disposition, the expenditure is made slowly but may be long continued.

It might be said that some of the toxemias and metabolic states produce lethargy rather than asthenia.

Objective asthenia, especially where the patient has become depressed over his inability to regain his normal state is often wrongly diagnosed as melancholia but melancholia is a distinct and well-defined mental disorder. In the second case described by Tastevin, the patient had been subject to attacks of asthenia lasting 6 to 9 months for over 40 years and at the age of 74, there was no weakening of her intelligence. Yet melancholia may be complicated by asthenia, and asthenia occurring in a weak organism may develop into melancholia.

In table I is given a list of the conditions and states which the various authors believe can produce asthenia. However, as Londe states, almost any lesion or even a slight and localized functional trouble may diminish muscular energy, and it is necessary to distinguish between those causing a true asthenia, those which by disturbing the metabolic processes produce a state of lethargy, and those which disturb the equilibrium of the vegetative nervous system. The problem is a complex one and the intricacy of body structure and function and the innumerable possible complications of disease make it difficult at times to decide just what is asthenia and what is not. For instance, included in the list are hypoglycemia

and diabetes. Hypoglycemia may be due to hepatic disorders, to hyperthyroidism, to hyperinsulinism from various causes, but among the most notable symptoms of hypoglycemia are mental confusion, epileptiform attacks, stupor, mania, etc. The manifestations of a moderate lowering of the blood sugar level are⁴⁰⁻⁵⁴

weakness
fatigability
pallor
sweating
restlessness
rapid pulse
muscular twitching
dilation of pupils
disturbed sleep
anxiety
ravenous hunger

Cannon, McIver and Bliss⁵⁵ explain that it is the sympathetic fibers which release glycogen from the liver and this reaction of sympathetic excitation is due to increased adrenal discharge in response to nervous impulses and is another remarkable example of automatic adjustments within the organism when there is a disturbance endangering its equilibrium. The mechanism protecting the body from hypoglycemia probably operates in two stages. A primary stage in which sympathetic activity with adrenal secretion occurs to mobilize sugar from the liver, and, if this proves inadequate, a secondary stage in which the activities of the first stage are intensified and augmented in convulsive seizures.

Diabetics complain of both weakness and depression yet the weakness may well be due to the inadequate diet or to the reaction of the sympathetic system to the hyperglycemia and the depression may be the result of a collec-

tion of partly metabolized products which will lead eventually to acidosis and coma. However, it is claimed, also, that the auto-intoxication of diabetes may act as a dysthenizing agent, in which case the asthenia should be distinguished from the other forms of weakness occurring during the course of the disease from other causes.

Colibacillosis is mentioned as a dysthenizing agent but Goiffon⁵⁶ has found cases where the colibacillosis as well as the asthenia (?) seemed to be the result of an underlying alkalosis.

Many authors believe that it is disturbances of the acid-base equilibrium acting on the vegetative system which causes asthenia, although there seems to be some confusion as to whether a predominating acidity or alkalinity causes vagotonia or sympathicotonia⁵⁷⁻⁶⁰. Goiffon finds that, in reality, alkalosis and acidosis are but two deviations of the normal equilibrium which, after reaching a certain point, produce analogous troubles. He believes, however, that the rôle of alkalosis in pathology is vast and lists the general findings about as follows:

TABLE VI

ALKALOSIS

lassitude (is common)
muscular weakness
drowsiness
loss of memory
headache with a tendency to vertigo
tachycardia
low arterial pressure
respiration is either slow or superficial,
ventilation is diminished, and the
pressure of carbonic acid is raised
digestive troubles are constant
hepatic insufficiency is very frequent
constipation with or without attacks of
diarrhea

sometimes there exists a diarrhea of fermentation with very acid stools and a relatively low level of total organic acids

urinary organic acids may reach three or four times the normal when the urine becomes alkaline, showing imperfect combustions

blood uric acid, lactic acid and oxalic acid are augmented

phosphaturia and alkalosis are almost always associated

a vegetable diet aggravates the condition by further alkalinizing the blood

Drouet⁶¹ in a discussion of the relation between the acid-base equilibrium and the equilibrium of the vegetative system, states that "anxiety" has long been catalogued as a manifestation of sympathicotonia and that the individuals show a permanent ionic alkalosis and a permanent hypoacidity of the urine, increased during the attacks. Guillaume (cited by Drouet) calls "anxiety" the morbid psychic tendency toward which the sympathetotonic inclines. Drouet states also that in epileptics there exists an habitual alkalosis even reaching a blood pH of 7.70, the number and intensity of the crises seem to vary with the alkalosis and in the intervals between the attacks the pH returns to normal. He cites Walther and Guillaume as having demonstrated that an epileptiform attack is the consequence of encephalic ischemia due to an energetic constriction of the arteries of the brain, that is, to a vascular sympathetotonia which extends also to the arteries of the cutaneous tissue causing pallor and to every arterial tree causing an elevation of the arterial tension before an attack and at its beginning. He believes that ophthalmic migraine is characterized by

sympatheticotonia in the form of arterial spasm and by blood alkalosis

Montassut and Delaville believe that the "constitutionally depressed" have a tendency toward a chronic alkalosis and that the inhibitions to which they are subject yield only after a certain amount of muscular activity has caused acidifying of the blood. Gorffon believes that the type of individual described above as the "hyposthenic" is really possessed of an alkaline diathesis or a predisposition to a permanent and constant alkalosis. Meyer⁶² believes that an abnormal alkalinity of the blood serum is the *primary* lesion in cancer which, in conjunction with certain other factors, favors the appearance of the cancer wherever a chronic local irritation is present. He reports cases of inoperable malignant tumor with metastases which were, to all appearances, cured by inducing acidosis and by keeping the pH at the normal level with hydrochloric acid and inhalations of O₂-CO₂ whenever a recurrence seemed likely.

The investigators who are interested in hypoglycemia say this is a very common finding and that wherever there is a state of notable weakness and easy fatigability a low blood sugar should be suspected. Those interested in alkalosis believe that in all states of slowed up energy, the trouble may be attributed to alkalosis. Likewise, those studying the rôle of the adrenals in the body economy, state that asthenia is the result of depleted function of the adrenal cortex. It is assumed that Crile's theory of adrenal-sympathetic overactivity as the cause of neurocirculatory asthenia refers to the adrenal medulla and an increased secretion of

adrenalin. But in Addison's disease, due to cortical deficiency, an entirely different state is produced which is also spoken of as asthenia.

TABLE VII

ADRENAL CORTX DEFICIENCY

general languor and weakness (asthenia is the cardinal symptom)
 low blood pressure
 pigmentation of the skin due to abnormal deposits of melanin, the normal cutaneous pigment
 gastrointestinal disturbances of varying severity
 vomiting is constant and sometimes uncontrollable
 anorexia
 nausea
 aversion to fat
 constipation
 acute gastric ulcers
 epigastric pain
 abdominal wall may be rigid and tender
simulating peritonitis
 loss of weight but it is noted that in a large percentage of cases the patients are overweight at the time of the first symptoms
 weak heart action
 vertigo and faintness on arising from bed
 hypothermia or fever
 nervous symptoms are numerous and prominent
 mental irritability
 restlessness
 areas of hyperesthesia
 hallucinations
 actual delirium and even acute mania
 convulsions
 coma
 nervous symptoms may be due to either anoxemia or to degenerative changes in the central nervous system
 cortical deficiency is caused by two principal pathological lesions, tuberculosis and simple atrophy, pigmentation is more often associated with atrophy

In this syndrome there are very few of the sympathetic symptoms which are so prominent in neurocirculatory asthe-

nia and in hypoglycemia while the vomiting suggests vagal predominance. The two significant findings from the standpoint of asthenia are the fatigue and the low blood pressure. Yet almost without exception, by the time these symptoms appear the adrenal tissue, of both medulla and cortex, has so degenerated that the patient survives only a few months at the most, while asthenia even of the objective type may exist for years and it is specifically stated that at autopsy no trace is left on the organism. In Addison's disease degenerative changes in the central nervous system are often noted in addition to those in the adrenal glands. Rogoff and Stewart^{10,63} believe that the low blood pressure in Addison's disease is probably a manifestation of intoxication. Rowntree⁶⁴ also states that there is much about the terminal picture in Addison's disease to suggest intoxication, affecting chiefly the central nervous system. Certain signs of intoxication were apparent in a series of seven cases reported by Hartman and his associates⁶⁵; laboratory examination showed a blood urea extending from 33 to 130 milligrams in five of the seven cases, and in two there was a leukocytosis of 14,000 and 21,600 respectively. The basal metabolic rate showed from 9 to 28 per cent decrease.

If it be true that the adrenal cortex is largely concerned in the destruction of products of metabolism and bacterial toxins and in furthering oxidation generally, any symptoms of intoxication following cortical deficiency are easily understood. But the point of interest in this discussion is whether this is a state of intoxication which is

to be differentiated from asthenia or whether the intoxication acts as one of the dysthenizing agents. In this connection, reference might be made to an article by Porritt⁶⁶ describing a type of lead poisoning in which the usual symptoms of plumbism are not exhibited. In these cases there is a slow, insidious saturation of the system over a long period of time by infinitesimal doses of lead contained, usually, in drinking water which is piped through lead pipes. The chief complaint of these patients is that they are "always tired." Porritt states that a strange *lethargy* creeps over the sufferer; he loses interest in life and feels a "weariness of flesh and brain." As the condition progresses, he becomes gloomy and taciturn; instead of joining in conversation with relatives and friends he sits silent and apathetic as if overcome by thoughts too melancholy to utter. His bowels are constipated and stubborn, he derives no satisfaction from his food and perhaps has abdominal discomfort which he puts down to indigestion. Sleep brings welcome respite but he gets up tired and weary in the morning. In neurotic females, emotional outbursts with flatulency and abdominal pain, may punctuate the melancholy. Lead is quickly excreted and the symptoms disappear when the cause has been removed.

The author states that in such cases the subject prefers sitting by the fire to making an effort of any sort yet when he forces himself through his tasks he finds no diminution of brain or bodily power. Feinblatt⁶⁷ in reporting a case of Addison's disease fol-

lowing tuberculosis of the vertebrae states that though the symptomatic asthenia was great, the power of the voluntary muscles to do work was normal. Cancer is mentioned in the table as one of the dysthenizing factors, but since all cancers do not cause asthenia it may be that it is the type of malignancy developing in a medium of chronic alkalosis which causes, not asthenia, but a similar state of intoxication. Such conditions not only poison the whole nervous system but in addition alter the internal chemistry and even the structure of the protoplasm of the cells.

Deschamps explains that there are three distinct conditions: (1) *Fatigue* which is the result of actual tiring, (2) *fatigability* which is anterior to fatigue and is a lowered work-tolerance, and (3) a *sensation of fatigue* which may exist independent of both fatigue and fatigability. A subject may be asthenic without experiencing the sensation of fatigue if he does not expend his capital of energy or he may experience the sensation of fatigue without being either fatigued or asthenic.

The numerous individuals who are called "lazy" undoubtedly experience the sensation of fatigue. Fuller⁶⁸ remarks that activity creates the capacity for further activity and that laziness is a purely mental condition with material physical consequences. It is the rapid distribution of oxygen to the tissues which constitutes healthy organic life. In anemia, where the reduced oxygen supply to the tissues is due to the diminished hemoglobin or erythrocyte count, a "lack of force" is also noted.

TABLE VIII

ANEMIA

easy fatigue and general lack of physical energy
 inability to stand prolonged mental and physical strain
 patients are never very ill and never very well
 they become breathless on the slightest exertion
 are nervous and worry over trifles
 there is impaired nutrition and weakened action of the heart muscle
 cold, and perhaps moist and clammy, hands and feet
 a tendency to chilblains
 gastritis is common in all forms of anemia and, in the extreme type, gastric ulcer
 there is a lowered resistance to even ordinary infections

All infections and intoxications may cause either anemia⁶⁹ or the syndrome of sympathetic instability so in the presence of an infective process, it will be a question of differentiating these two forms of weakness from asthenia.

If one wishes to assume that all conditions causing a lack of force or strength should be considered "asthenia" the problem might be solved by stating, as does Deschamps, that there are asthenias of production and asthenias of distribution. The asthenias of production would include all the states of weakness, fatigue, depression and lowered resistance caused by the various physicochemical disturbances, glandular disorders, malnutrition, anemia, toxic-infections or any other factors which interfere with metabolism and the production of energy. Asthenias of production would include also all the constitutional states the 50 and 75 per cent individuals, where the organism is not equipped to produce sufficient energy.

The same author uses a slightly different classification as follows

Asthenias of insufficiency where there is an inadequate supply of energy produced
 Asthenias of exhaustion where the supply has been exhausted as in convalescence or perhaps in neurasthenia

Asthenias of inhibition where there is an obstacle in the nervous system which prevents the transmission of energy

Deschamps states, however, that to call every diminution of energy "asthenia" is a misinterpretation and most of the other authors agree that asthenia is strictly autonomous and that the term should be confined to the "asthenias of inhibition" where there is an arrest of the transmission of energy

TREATMENT

Except in the constitutional cases, asthenia occurring in the absence of a definite dysthenizing agent is probably rare. Asthenia is an effect rather than a cause. Benon finds that asthenia complicates a great number of disease states, that ordinarily it is of neither diagnostic nor therapeutic interest and when the dysthenizing cause has disappeared the neurosthenic equilibrium will right itself. Deschamps says that the most curious symptomatic consequence of all types of asthenia is the impossibility for the patient to accumulate energy, regardless of all pharmacological and dietary measures.

Ballet states that in some cases the asthenia develops in the course of convalescence but most often it makes its appearance when the general health of the patient seems to have been restored. The case of intercostal neuralgia cited above is an excellent example, the patient was supposed to have recovered

from her illness when almost without warning she found herself without sufficient nervous force to make the least effort. For this type of asthenia, time and proper hygiene are the only requirements, immediate and absolute repose in bed is the primary consideration since forced effort or activity of any sort, by aggravating the asthenia, may change a temporary and unimportant complication into a state of permanent semi-invalidism. Among the numerous cases of post-influenzal asthenia, it is not unusual to observe individuals who are making an attempt to follow their normal daily routine, whether this be assuming the responsibilities of a household or engaging in business. Their friends will remark that at times they seem scarcely to have the strength to move one foot ahead of the other. In many instances, this permanent state is undoubtedly the result of a too early return to active life, with the patient forcing himself to disregard this seemingly inexplicable lack of strength. Most physicians are coming to realize the necessity for an adequate period of convalescence after acute fevers and infections, but it does not seem to be generally understood that it is because the neurosthenic function may be temporarily suppressed by the disease process.

When, as the result of forced effort during a temporary asthenia, or following trauma or emotional shock, either a permanent and incurable state or a prolonged attack of asthenia has been installed, treatment must consist mainly of the usual hygienic measures for building up the organism, with especial attention to the three fundamental principles of rest, nutrition and

elimination In these cases, because of the relaxation of the digestive tube, there may be intestinal auto-intoxication or a tendency toward alkalosis. Foci of infection in the upper respiratory tract and teeth, thorax, abdomen or pelvis or any organic trouble should be thoroughly searched for and eradicated.

It is important to determine the gastric tolerance and arrange the diet accordingly. Usually the diet will be limited to bland, easily digested foods apportioned, if necessary, into five light meals to avoid burdening the stomach too much at one time.

Physical therapy in the form of cabinet baths, pressure sprays, light massage, ultra violet rays or diathermy will prove of value in eliminating poisons and improving the circulation, and in addition will have a good psychological effect. This form of therapy is especially valuable in cases of subjective asthenia.

Deschamps believes that where the cerebral centers are deficient, there will be an associated mineral insufficiency, especially of magnesium and phosphorus, the loss of these two minerals is the surest sign of nervous deficiency. He believes the best way to reconstitute an asthenic is to give combinations of magnesium with phosphates. Phosphorus in the form of glycerophosphates is also extensively used. Small amounts of arsenic or strychnine may be given for short periods although drugs with a tonic or stimulating effect are not well tolerated as a rule.

Wakefulness and persistent insomnia are ordinarily best combated by varying combinations of tincture of

valerian, elixir triple bromides and elixir phenobarbital. The use of these drugs in equal portions and in adequate amounts is satisfactory. For extreme cases, occasional resort to codeine sulphate, gr $\frac{1}{4}$ to $\frac{1}{2}$, may be necessary once or twice in the early hours of the night to establish the somnolent state.

A certain experience with liver extract indicates that this preparation may have some substantial therapeutic value in returning the asthenic individual to his normal power although the mode of action is not known. It is our practice to recommend a tablespoonful of liquid liver extract 3 or 4 times daily for 3 to 6 weeks. Response, as indicated by an increase in the general well-being, has been noted in approximately 90 per cent of the patients so treated. While we have not yet had the opportunity of proving the efficacy of adrenal cortex hormone in the treatment of asthenia, this drug also gives promise of being valuable in certain cases. These two preparations would be expected to act by improving the general metabolism and by raising the erythrocyte count and hemoglobin and not by any direct influence on the deficient nerve center. However it is always possible that a secondary hepatic or adrenal insufficiency may have developed after an extended period in a state of objective asthenia, in which case the above remedies might have a specific effect.

Since the physicochemical state of the organism is of such significance in making a differential diagnosis and in indicating the therapeutic procedure, the required laboratory examinations should be made to detect any devia-

tions from the normal in the chemistry of the blood and urine. Where there are evidences of gastric hypoacidity, urinary hypoacidity, blood alkalosis, high blood calcium, or any other findings which suggest sympathetic predominance, vagotonic substances might be given to stimulate the parasympathetic. Various researches now being conducted indicate that posterior lobe pituitary preparations by acting on the vagus may be of value in producing gastric motility and secretion.⁷¹

Endocrine preparations such as desiccated thyroid substance, whole ovary substance, corpus luteum, adrenalin, pituitrin and the numerous modifications and combinations of these, have been tried with varying degrees of success. We have noted, especially in treating obese female patients with whole ovarian substance to which has been added 1/10 to 1/12 grain of thyroid extract, that a general increase in power has been obtained.

Ballet believes that the degree of asthenia probably has a relation to the degree of native insufficiency and where there are fundamental morphological and functional defects, a superimposed asthenia will be more exaggerated and more difficult to treat. Where pronounced psychic disturbances are present, the aid of the neurologist must be sought. In all cases of asthenia, however, the psychological background and the environment of the patient must be carefully studied from the standpoint of both diagnosis and treatment.

In the case of constitutional asthenia, the best advice would seem to be for the individuals to stop trying

to develop themselves to normal physical and nervous capacity, but to determine what their maximum abilities are and keep slightly under that limit.

TABLE IX

PRINCIPLES OF TREATMENT

- 1 *Repose (the primary and fundamental treatment for asthenia)*
Physical, intellectual and emotional forcing the patient to activity of any sort will aggravate the asthenia and cause it to become permanent.
After a more or less prolonged period of rest, muscular and mental activity may be gradually resumed, but this should not be permitted until the evolution toward cure is certain.
- 2 *Explain this peculiar form of weakness and its probable future course* not only to the patient but to his family since it is usually the relatives and friends who urge the patient to exercise and move about in order to regain his strength.
- 3 *Make a thorough search for foci of infection or organic troubles* which may be the cause of the asthenia.
- 4 *Institute the required laboratory procedures* for the detection of deviations from the normal in the physico-chemical state of the organism.
- 5 *Diet*
Give high caloric foods which are easily masticated and easily digested.
It may be necessary to increase the number of meals in order not to burden the stomach too much at one time.
In the acute stage, a milk, or milk and vegetable, diet may be temporarily indicated.
Wine may be beneficial for its mild tonic action and food value, and for raising the erythrocyte count and hemoglobin.
- 6 *Physical therapy*
Very light massage
Ultra violet light and diathermy

In the chronic cases or in the case of subjective asthenia, cabinet baths, pressure sprays, hydrotherapy, etc are of great benefit

7 Drugs

Avoid drugs in general

At times, harmless doses may be given for their psychological effect Sodium bromide is especially successful in gastric asthenia

Glycerophosphates and combinations of magnesium and phosphorus may be prescribed for the nervous deficiency

Strychnine and arsenic may be given in small doses for short periods to the calm, depressed type but will lead to aggravation in the patient with a tendency to "unnerving"

Give sedatives for insomnia

Avoid cathartics with drastic action or which cause intestinal irritation

Adrenal cortex preparations, liver extract, thyroid and ovarian substance, adrenalin, pituitrin, etc may be helpful in overcoming the asthenia

Where there is evidence of sympathetic predominance, give parasympathetic stimulants

NEURASTHENIA

In the treatment of neurasthenia, Beard states that to devote the whole attention to special and local phases such as spinal or cerebral irritation, asthenopia, oxaluria, insomnia or nervous dyspepsia can never be successful The treatment should be constitutional with special attention to local manifestations whenever they become severe but no two cases will be alike in all details Where the subject is under treatment for a long period of time, Beard advocates giving a sedative treatment one week, a tonic the second and the third to do nothing at all Sometimes suspending treatment acts as a therapeutic measure in itself

In his experience, the combination of electricity, massage, counterirritants and various sedative-tonic medications seemed to obtain the best results

In cerebraesthesia as vigorous outdoor exercise as the patient can stand should be prescribed, in myelasthenia, especially in women, absolute rest in bed in quiet, if not darkened, rooms is necessary In digestive hygiene some need to be cautioned against overfeeding and some must be coaxed to eat more than has been their custom A milk diet may be required in some cases and in others small frequent meals of light food According to Deschamps, neurasthenics and also asthenics possess an "irritable" weakness and on the ingestion of irritating foods or medications an atonic and hypoacid stomach may quickly become hypertonic and hyperacid This irritable weakness extends to the whole organism, including the psychic apparatus

In neurasthenia the psychology of the patients is of the utmost importance Neurasthenics as a rule take a great interest in their distresses and relate their pains and symptoms in detail Beard found that the greater the amount of intellect and the less the emotional element, the better the prognosis would be

While in psychasthenia and neurocirculatory asthenia the fundamental etiology is different, nevertheless the therapeutic measures recommended above will undoubtedly have some beneficial influence in returning the individuals to a normal state

CONCLUSIONS

There appears to be a regulating neurosthenic mechanism located in the

brain which ordinarily maintains each subject in an eusthenic state. The varying degrees of sthenia, asthenia and hypersthenia may be regarded as the "neurosthenic state" of an individual in contrast to the state of physical strength dependent upon size and development, nutrition, hygiene, etc.

The neurosthenic equilibrium may be disturbed by a number of factors known as "dysthenizing agents," and an abnormal asthenia or hypersthenia may result. The most common of the dysthenizing factors are pain, emotional shocks, trauma to any part of the body with an associated total loss of consciousness, sunstroke, acute and chronic infections and intoxications such as influenza and grippe, typhoid fever, tuberculosis or malaria, streptococcic infections or food poisoning.

A differential diagnosis is of the utmost importance since muscular energy may be diminished by a number of factors and states produced which at times may be difficult to distinguish from asthenia.

Asthenia occurring as a complication of various disease states is of no especial significance and will disappear when the neurosthenic equilibrium has righted itself. Immediate and absolute repose in bed and proper hygiene are the only therapeutic requirements.

Forced effort or activity of any sort, by aggravating the asthenia, may change a temporary and unimportant complication into a state of permanent and incurable semi-invalidism, as may be observed in the innumerable post-influenzal cases where the patients, because they disregarded the asthenia and forced themselves to return too soon to an active life, have never since been able to regain their normal state.

In order to carry on, these individuals must recognize their physical and mental capacity and limit their activities at a point just under their maximum ability. Small amounts of drugs with a mild stimulating or tonic action or light wine may be given; various combinations of phosphates for the nervous deficiency, biological preparations such as liver extract, adrenal cortical hormone, ovarian, thyroid and pituitary substance, and physical therapy may be of value in overcoming the asthenia.

A study of this subject suggests that, due to the high tension living of the present age, the traumas, emotional shocks, familial and financial cares and the waves of infection which seem to spread over communities, the profession must be prepared to encounter a state of asthenia more frequently than has been the case in the past.

REFERENCES

- ¹DANO, La douleur gastrique et l'asthénie, *Rev. gen. de clin. et de therap.*, 1930, xlv, 657-663.
- ²LOPIER, M., et BAUMANN, J. La leias-thénie, *Presse méd.*, 1929, xxxvii, 1165-1167.
- ³FRANCK, C., et JEAN-GALLOIS. Contribution à l'étude des hypotonies, astigmatisme, asthénie, hypotension artérielle, *Presse méd.*, 1931, xxxix, 918-921.
- ⁴BRACHET, J. L. *Memoire sur l'asthenie* 1829, Gabon, Paris.
- ⁵LONGE, P. L'asthenie, *La Semaine méd.*, 1905, xxv, 157-160.
- ⁶BENOX, R. L'asthenie en clinique nerveuse et générale, *Bull. méd. Paris*, 1928, xlii, 39-42.
- ⁷TASTEVIN, J. L'asthenie post-douloureuse

- et les dysthénies périodiques, psychose périodique *Ann med psychol*, 1911, xiii-xiv, 18-35 Part I, Pathologie, 1911, xiii, 177-200
Part II, Les dysthénies périodiques, 1911, xiii, 384-402
Part III Suite et fin, 1911, xiv, 18-35
- ⁸ANDREWS, C L Grippal infections Post-febrile cardiovascular disturbances, usually unrecognized report of cases, *Jr Am Med Assoc*, 1931, xcvi, 1791-1794
- ⁹BENON, R L'asthénie chez les enfants, *Arch de med d'enfant*, 1926, xxix, 525-531
- ¹⁰ROGOFF, J M, and STEWART, G N Suprarenal cortical extracts in suprarenal insufficiency (Addison's disease), *Jr Am Med Assoc*, 1929, xcii, 1569-1571
- ¹¹BENON, R Asthenie et hypersthénie juveniles curables, *Bull Soc clin de med ment*, 1927, xv, 113-116
- ¹²MICHON, P La jeune mere asthénique, *Presse med*, 1928, xxxvi, 732-733
- ¹³MONTASSUT, M, et DELAVILLE, M La depression constitutionnelle, asthenie, emotive, déséquilibre physico-chimique, *Presse med*, 1931, xxxix, 774-776
- ¹⁴BENON, R La neurasthenie vraie, diagnostic et traitement, 1926, Libr, A Maloine, Paris
- ¹⁵BEARD, G M, and ROCKWELL, A D A practical treatise on nervous exhaustion, (neurasthenia), its symptoms, nature, sequences, treatment, 1901, E B Treat & Company, New York
- ¹⁶BALLT, G, and SMITH, P C Neurasthenia, 1911, Wm Wood & Co, New York
- ¹⁷HURRY, J B The vicious circles of neurasthenia and their treatment, 1915, J & A Churchill, London
- ¹⁸ASCHAFFENBERG, G Psychasthenic states Curschmann's Text-book on nervous diseases, 1915, P Blakiston's Son & Co, Philadelphia, ii, 841-923
- ¹⁹WEISENBURG, T H, YASKIN, J C, and PLEASANTS, H Neuropsychiatric counterfeits of organic visceral disease, *Jr Am Med Assoc*, 1931, xcvi, 1751-1757
- ²⁰RILSMAN, D Acute psychoses arising during the course of heart disease, *Am Jr Med Sci*, 1921, clxi, 157-162
- ²¹FOSTER, N B Psychic factors in the course of cardiac disease *Jr Am Med Assoc*, 1927, lxxxix, 1017-1018
- ²²HEAD, H Certain mental changes that accompany visceral disease, *Goulstonian Lectures for 1901*, Part III, *Brain*, 1901, xxiv, 345-429
- ²³PRATT, J H, GOLDEN, L A, and ROSENTHAL, J The psychalgias A study of their frequency and characteristics by means of the procaine skin test and by the effect of suggestion, *Jr Am Med Assoc*, 1932, xcvi, 441-446
- ²⁴JANET, P Les obsessions et la psychasthenie, 1903, Germer Bailliere et Cie, Paris
- ²⁵CURSCHMANN, H Text-Book on nervous diseases Translated by C W Burr, 1915, P Blakiston's Son & Co, Philadelphia, ii, 1068-1096
- ²⁶ROTHSCHILD, M A Neurocirculatory asthenia, *Bull N Y Acad Med*, 1930, 2nd Ser, iv, 223-242
- ²⁷ROBEY, W H, and BOAS, E P Neurocirculatory asthenia, *Jr Am Med Assoc*, 1918, lxxi, 525-529
- ²⁸HIRSCHBOECK, F J Treatment of functional heart disease, *Jr Am Med Assoc*, 1928, xci, 1852-1857
- ²⁹MACFARLANE, A Neurocirculatory myasthenia A problem of the sub-standard soldier, *Jr Am Med Assoc*, 1931, lxxi, 730-733
- ³⁰KERLEY, C G The effort syndrome in children, *Arch Ped*, 1920, xxxvii, 449-454
- ³¹DA COSTA, J M On irritable heart, a clinical study of a form of functional cardiac disorder and its consequences, *Am Jr Med Sci*, 1871, li, 17-52
- ³²LEWIS, T The soldier's heart and the effort syndrome, 1919, Paul B Hoeber, New York
- ³³CRILE, G Denervation of the adrenal glands for neurocirculatory asthenia, technique and clinical results, *Surg Gynec & Obst*, 1932, xlii, 294-298
- ³⁴SMICI, D, POPESCU, M, et SANDULESCU Recherches sur l'etiology de l'instabilité cardiaque tachycardique permanente à l'aide du métabolisme basal associé à

- l'épreuve de Mico, Arch d mal du coeur, 1931, xxiv, 539-553
- ³⁵MERCIER, M Le syndrome hyposthénique, Rev gén de clin et de thérap, 1927, xli, 357-360
- ³⁶GRIFFITH, J Q The frequent occurrence of abnormal cutaneous capillaries in constitutional neurasthenic states, Am Jr Med Sci, 1932, clxxxiii, 180-187
- ³⁷LEVISON, L A Autonomic imbalance and hyperthyroidism, Ohio State Med Jr, 1930, xxvi, 913-921
- ³⁸BARKER, L F The diagnosis and treatment of the milder affective disorders (depressions and elations), Canad Med Assoc Jr, 1932, xxvi, 273-277
- ³⁹BORTZ, E L Visceroptosis, its clinical significance and treatment, Am Jr Med Sci, 1930, clxxx, 59-71
- ⁴⁰DESCHAMPS, A, and VINCHON, J Les maladies de l'énergie Les asthénies et la neurasthénie, 1927, Felix Alcan, Paris
- ⁴¹CANNON, W B Bodily changes in pain, hunger, fear and rage, 1915, D Appleton and Co, New York
- ⁴²CANNON, W B The sympathetic division of the autonomic system in relation to homeostasis, Arch Neurol and Psych, 1929, xxii, 282-294
- ⁴³BARD, P The central representation of the sympathetic system as indicated by certain physiologic observations, Arch Neurol and Psych, 1929, xxii, 230-246
- ⁴⁴HUBER, C G, and CROSBY, E C Somatic and visceral connections of the diencephalon, Ibid 187-229
- ⁴⁵DANIELOPOLU, D Les trois lois fondamentales qui régissent le fonctionnement du système nerveux végétatif à l'état normal et pathologique, Presse méd, 1928, xxxvi, 1645-1647
- ⁴⁶PENDE, N; NACCARATI, S, and DRAPER, G Constitutional inadequacies, 1928, Lea & Febiger, Philadelphia
- ⁴⁷GAPROD, A E The inborn factors in disease, 1931, Clarendon Press, Oxford
- ⁴⁸DRAFTER, G Disease and the man, 1930, The Macmillan Company, New York
- ⁴⁹ALLAN, F N Hyperinsulinism, Arch Int Med, 1929, xlv, 65-70
- ⁵⁰CARR, A D Neurologic syndromes associated with hypoglycemia, Jr Am Med Assoc, 1931, xcvi, 1850-1852
- ⁵¹HOLMAN, E F Hypoglycemia in exophthalmic goitre, Bull Jr Hop Hosp, 1923, xxxiv, 69-70
- ⁵²YASKIN, J C Nervous symptoms as earliest manifestations of carcinoma of the pancreas, Jr Am Med Assoc, 1931, xcvi, 1664-1668
- ⁵³ALLAN, F N Hyperinsulinism, Arch Int Med, 1929, xlv, 65-70
- ⁵⁴CARR, A D Neurologic syndromes associated with hypoglycemia, Jr Am Med Assoc, 1931, xcvi, 1850-1852
- ⁵⁵CANNON, W B, McIVER, M A, and BLISS, S W Studies on the conditions of activity in endocrine glands XIII A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia, Am Jr Physiol, 1924, lxix, 46-66
- ⁵⁶GOIFFON, R Alcalose et diathèse alcaline, Presse méd, 1928, xxxvi, 1109-1111.
- ⁵⁷LAIGNEL-LAVASTINE, M Vagotonie et alcalose, Ibid 1233
- ⁵⁸OLIVIER, H R La médication organo-végétative, Jr méd franç, 1927, xvi, 75-80
- ⁵⁹TINEL, J, and SANTENOISE, D Vago-sympathique et choc anaphylactique, Jr méd franç, 1922, xi, 106-110
- ⁶⁰RICHER, C, fils, and GODLEWSKI, H Causes, diagnostic et mécanisme des chocs, Jr méd franç, 1922, xi, 111-116
- ⁶¹DROUET, G Équilibre acido-basique et équilibre vago-sympathique. Jr de méd de Paris, 1930, I, 959-960
- ⁶²MEYER, W The acidosis treatment of inoperable malignant tumors, Am Jr Surg, 1932, xv, 112-119
- ⁶³ROGOFF, J M Diagnosis and treatment of Addison's disease, Canad Med Assoc Jr, 1931, xxiv, 43-51
- ⁶⁴ROWNTREE, L G Addison's disease The cyclopedia of medicine, 1931, F A Davis Co, Philadelphia, I, 139-152
- ⁶⁵HARTMAN, F A, THORN, G W, LOCKIE, L M; GREENE, C W, and BOWEN, B D Treatment of Addison's disease with an extract of suprarenal cortex (Cortin), Jr Am Med Assoc, 1932, xcvi, 788-793
- ⁶⁶PORRITT, N Cumulative effects of infinitesimal doses of lead, Brit Med Jr, 1931, II, 92-94

- ⁶⁷FEINBLATT, H M Three cases of endocrine disease with pronounced asthenia, *Med Clin N Am*, 1928, xi, 1071-1079
- ⁶⁸FULLER, A W Anæmia Its causes and modern treatment with a chapter on neurasthenia, 1924, H K Lewis & Co Ltd, London
- ⁶⁹CAREY, J B, and TAYLOR, J H Primary aplastic anemia, a discussion and report of two cases, *ANN INT MED*, 1931, v, 471-477
- ⁷⁰BENON, R Le traitement général de l'asthénie, *Jr de med et chir prat*, 1930, ci, 585-608
- ⁷¹BEATTIE, J Relation of the tuber cinereum to gastric and cardiac function, *Canad Med Assoc Jr*, 1932, xxvi, 278

The Clinical Study of the Atrophic Tongue

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THE bald tongue has been recognized for many years by clinicians. Its association with anemia was probably first appreciated in 1846 by Dawson¹. In 1909 William Hunter² concluded an argument for the infectious origin of the glossitic, gastric and intestinal lesions of pernicious anemia with the statement "that the most important of these signposts (glossitic) is the one which can be earliest recognized and kept in sight from the first to the last". The strength of this position was universally conceded by students of the subject, but renewed interest in and attention to the close scrutiny of the tongue in pernicious anemia arose from an appreciation of the remarkable transformation in its surface markings that attended liver therapy. Furthermore a peculiar glossitis with ultimate atrophy has been described in a wide series of clinical entities, and from this analogy a possible interrelationship is receiving increasing consideration.

This growth in the clinical importance of the subject impressed the

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need for an objective method of preserving the changing picture of the lingual markings. The methods pursued are recounted elsewhere³. After devious trials smoked paper, as suggested by Isaacs, Sturgis, and Smith,⁴ afforded the best results (figure 1). With practice a quite constant technic was developed; and dipped in shellac these tongue prints constitute permanent records of inestimable service in evaluating progress.

Particular interest in the present relation attaches to the study of the lingual changes in pernicious anemia. Hunter² characterized the histologic picture as of an acute and subacute inflammatory nature succeeded by degenerative and atrophic changes. Round-celled infiltration in the tissues and the walls of the blood vessels of the tongue mark the inflammatory stage, whereas atrophy of the epithelium succeeds necrosis and mucoid degeneration. In the late stage a thin fibrous sheet replaces the epithelium and deeper penetration of connective tissue into the musculature indicates the extent of the preceding inflammatory process. The actual total mass of the tongue is reduced through muscular as well as epithelial atrophy.

An advanced stage in the glossitic picture is represented by

Case I, C F, a white farmer aged 54 years, who was readmitted in the second relapse of pernicious anemia, December 1, 1931. Combined degeneration of the cord had been established on the earlier admission 4½ years previously, but the hematopoietic response to liver had been satisfactory and many of the signs of neurologic involvement had disappeared with improved strength and muscle tone, so that on his return to the farm the patient had been able to resume his work. An injury to the left ankle eight weeks prior to readmission initiated a de-

Soreness of the tongue is a common complaint among patients suffering from pernicious anemia. Yet a minority of these patients may entirely escape this subjective discomfort. Disturbances of taste are less common. Characteristic is the marginal injection of the tongue with tiny vesicles here and at the tip. These vesicles tend to rupture and leave denuded areas. The beefy redness and vesiculation are



FIG 1 Contrasting a photograph and a smoked paper print of a glossitic tongue with some degree of atrophy, taken on the same day

cline which was marked by weakness, breathlessness, paresthesias and rectal incontinence. Neglect of liver therapy was admitted. Gross evidence of cord involvement was established in absent deep tendon reflexes in the legs, loss of vibratory and position sense, ataxia in all test movements and lack of sphincter control. The tongue was completely bald and glistening. The hemoglobin registered 45 per cent and the erythrocytes 1.8 million on admission. Bronchopneumonia terminated life before liver therapy and transfusions could effect any appreciable change in the blood picture. Of particular interest in the necropsy findings was the hyperplastic bone marrow. The histologic study of the tongue (figures 2 and 3) revealed a total absence of papillae. The epithelium was thinned in areas and there was marked round-celled infiltration beneath the epithelium as well as about the smaller arterioles.

periodic and shifting in occurrence. Succeeding this stage of inflammation, denudation is the rule, but there is no relation between the severity of the inflammation and the degree of the ultimate atrophy of the papillae, nor does the former give any prognostic information as to the time of appearance of the latter. Hunter² recorded the occasional subsidence of the acute glossitic manifestations with the advance of the anemia, but added that in other cases such was not the case until atrophy of the papillae was complete. Not infrequently glossitis may antedate the anemia. In other individuals with advanced anemia the tongue changes may be insignificant.

As has been remarked, the introduction of liver into the therapy of pernicious anemia completely altered the sequence of events. Minot and Murphy⁵ noted that "the distressing tongue symptoms so characteristic of pernicious anemia usually vanished soon after liver was taken. Vesicles on the edges and tip of the tongue disappeared as did the red-streaked, raw, or beefy appearance. The sense of rawness or pain in the esophagus subsided. In a few patients who had

a pronounced disorder of the central nervous system, the disappearance of the tongue symptoms and signs was less rapid. In none of the patients who have continued the diet well have the tongue symptoms either persisted or returned. Within a few months the tongue has usually lost its shiny appearance entirely and has appeared normal."

An unusual experience is cited in Case II.

A. H., a white laborer aged 62 years, was



FIG. 2 Microscopic appearance of the glossitic tongue of Case I (low power—x 70)
(Courtesy of Dr. Gorton Ritchie)

elsewhere reported as a typical example of the recidivistic tendency of certain pernicious anemia patients under liver therapy. Beginning with his original admission, February 15, 1927, each of five successive relapses was attended by erythrocytic counts ranging from 740 thousand to 1.35 million. Not until his last two admissions of December 14, 1929, and November 20, 1930, was there the slightest evidence of neurologic involvement as manifested by a debatable obtunding of the vibratory sense in the left lower leg. On each occasion of relapse the tongue showed marked atrophy of the papillae to complete baldness. Improvement in the lingual condition anticipated the complete

blood remission. In the four periods of observation where accurate notes of the return of papillae to the tongue were made, the hemoglobin and erythrocyte figures were 60 per cent with 4.07 million, 58 per cent with 3.37 million, 55 per cent with 3.83 million, and 55 per cent with 3.65 million, respectively, at the time of papillary reappearance.

The relatively close coincidence of these figures stimulated a study of this detail, but the circumstance is apparently strictly individual and dependent upon other factors than hemoglobin



FIG. 3. Microscopic appearance of the tongue of Case I (high power— $\times 240$). Courtesy of Dr. Gorton Ritchie.)

and erythrocyte levels. In this particular instance the normal surface markings were always restored to the tongue before the blood reached a satisfactory level. Because of the patient's low mentality no accurate information was afforded of the chronologic order of glossitic symptoms and hematopoietic decline upon neglect of liver therapy. At no time during hospitalization were there evidences of acute glossitis.

The tongue prints have afforded accurate records in following the progress of the glossitic changes in pernicious anemia under liver therapy. From the evidence now available, the filiform papillae first disappear, particularly from the tip and the edges of the tongue. Thereafter the fungiform papillae are lost. The position of the circumvallate papillae renders their inclusion in tongue prints of this order impracticable, but apparently they escape gross involvement even in severe degrees of glossitic atrophy—a circumstance which may explain the preservation of the gustatory sense in

many patients with pernicious anemia under such conditions. The tongue markings frequently begin their return toward normal long before the general and the hematopoietic responses to liver or its equivalent have been satisfactory, as related in Case II. The order of visible return of the papillae is the reversal of their order of disappearance. The fungiform papillae usually become distinctly prominent and then the filiform projections rapidly fill in the intervening spaces to render the fungiform papillae much less evident. The transformation of the smooth, glistening tongue of pernicious anemia to a normally surfaced member is a striking objective result of liver therapy (figure 4), but there is no apparent parallelism between the lingual and the hematopoietic responses to this form of treatment. The tongue may return to apparent normality as early as two weeks after the institution of adequate liver therapy.

Wider experience has refuted the assertion of Minot and Murphy⁵ rela-

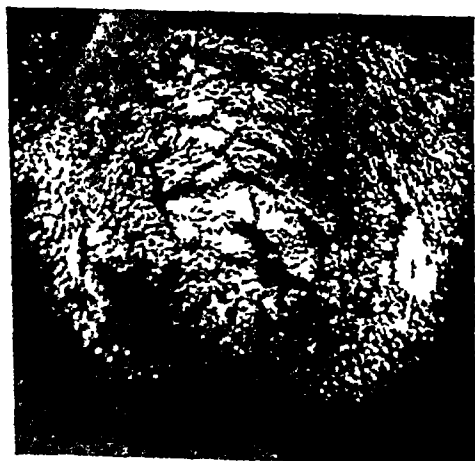


FIG. 4. Illustrating return of filiform papillae in the atrophic tongue. The filiform papillae in the second print almost obscure the fungiform elements which are so prominent in the first print.

tive to the permanency of the glossitic remission. In an overwhelming majority this advantage is maintained, provided the dosage of the effective maturing factor is held at a sufficiently high level. Most of the recurrences of glossitic manifestations in the Wisconsin General Hospital have attended efforts to establish the maintenance dosage of liver or its equivalent by gradual withdrawal, or an intercurrent infection which has reduced the efficacy of a previously adequate dosage. Isaacs⁶ has made an especial study of the cyclic trend of relapses in pernicious anemia. In periods of seasonal depression glossitis of a mild order may, in his opinion, recur as a manifestation of such a relapse. As a rule, regardless of the background, the lingual changes may be controlled by increasing the amount of liver exhibited, although Isaacs, Sturgis and Smith⁷ feel that "the ingestion of liver does not seem to be entirely specific for this symptom."

Second in order of frequency as a cause of the atrophic tongue in temperate climates comes simple achlorhydric anemia of which Case III is a classical example.

Case III Mrs. A. E., a white housewife, aged 44 years, was admitted primarily for a chronic arthritic affection. The inventory by systems afforded some insight into vague digestive disturbances with intolerance for pork and onions. For nine months little meat had been eaten but the patient had partaken abundantly of fresh vegetables. Soreness of the tongue and mouth had been remarked for several months when "acid" foods were eaten. Citrus fruits would occasion serious distress, but lettuce and butter were craved. The menstrual cycles were regular. Of particular interest in the present relation were the physical observations of pallor and lingual atrophy. The tongue was raw in ap-

pearance and practically devoid of papillae. On admission the hemoglobin was 50 per cent and the erythrocytes 4.1 million. No free hydrochloric acid was demonstrable in the gastric contents even after histamine injection.

A conclusion of simple achlorhydric anemia was derived and the therapeutic trial of liver extract initiated. After two weeks of liver extract in adequate doses the hemoglobin was 45 per cent and the erythrocytes 4.2 million. Thereupon the treatment was shifted to Bland's mass 4 grams daily and diluted hydrochloric acid 4 cc three times a day. The gain both from a clinical and from a laboratory standpoint was progressive from this time, so that two months later the hemoglobin registered 85 per cent and the erythrocytes 5.6 million. A month after the initiation of iron and hydrochloric acid therapy there was first noted a return of papillae to the anterior portion of the tongue. At this time the hemoglobin was 57 per cent and the erythrocytes 4.52 million. Clearly the lingual improvement anticipated any appreciable amelioration in the blood picture.

Simple achlorhydric or microcytic anemia has received wide attention in the recent medical literature at the hands of Kaznelson,⁸ Watkins,⁹ Witts,^{10, 11} and others. Witts¹⁰ reported glossitis in 25 per cent of 50 cases of simple achlorhydric anemia. The frequency with which frank changes to inspection were unattended by subjective complaint, led him to the conclusion of a much higher incidence. The clinical course of the glossitis to its ultimate atrophic stage can scarcely be distinguished from similar changes in pernicious anemia. In a series of cases under observation at the Wisconsin General Hospital the response to iron and diluted hydrochloric acid in full doses has followed the course of Case III. Occasional instances of simple achlorhydric anemia have been

encountered in which there has been no return of the lingual papillae in spite of a complete remission in the blood picture. The impression gathers that the lingual and the pharyngeal manifestations of this condition are much less amenable to treatment than the analogous states in pernicious anemia. Liver has not been effective in the treatment of simple achlorhydric anemia.

A somewhat less frequent situation attended by the atrophic tongue is represented in Case IV.

Case IV Mrs M P, a white housewife aged 41 years, complained of choking and difficult swallowing. A "nervous" constitution had given way to emotional outbursts over a period of four or five years. Vasomotor instability was evinced in hot flashes. For 1½ years inexplicable attacks of dyspnea had occurred paroxysmally without reference to effort. A sensation of tightness in the throat with occasional inability to swallow comfortably had recurred at intervals for ten years and more recently had lead to choking. Preceding the dysphagia for about ten years the patient had experienced repeated soreness of the tongue. In her judgment both of these conditions were becoming progressively worse. Pertinent to the present consideration were the marked pallor of the skin and mucous membranes, the atrophic tongue and the palpably enlarged spleen. From time to time during the hospital stay superficial apthae appeared in the mucous membranes of the nose and throat. The hemoglobin was 48 per cent and the erythrocytes 4.2 million on admission. The icterus index was 5 and the stools showed no ova nor parasites. There was no urobilinogen in the urine. The basal metabolic rate was determined as -3 and -2. Inability to pass the stomach tube precluded a determination of the acidity of the gastric contents.

This case fulfilled the diagnostic criteria of the Plummer-Vinson syndrome. Accordingly a close inquiry was made into her dietary and no essential principle was found lacking. Milk, cream and butter were taken

adequately, whereas eggs were not well tolerated. Fruits, except the citrus variety, and greens were enjoyed. Citrus fruits seemed to aggravate the soreness of the tongue and the dysphagia. Cereals, vegetables and puddings ranked as favorite foods. Meat was eaten sparingly, but the patient professed an appetite for the fat of meats as well as for butter. She volunteered the information that she had always been anemic and had taken "blood" medicine as long as she could remember.

After two weeks of Bland's mass 4 grams daily and diluted hydrochloric acid 6 cc three times a day, the hemoglobin rose to 70 per cent and the erythrocytes to 5.49 million. Coincident with the improvement in the blood picture the dysphagia became decidedly better and papillae returned to the tongue.

The so-called Plummer-Vinson syndrome was first described by Vinson¹² in 1922, since which time the literature has contained scattered references to the subject. (H S Plummer had applied the term hysterical dysphagia to this condition in 1914.) The majority of these contributions have merely added further examples of the condition or have sought to explain this obscure syndrome of glossitis, dysphagia and anemia, which usually responds miraculously to the passage of the esophageal sound. Moersch and Conner¹³ reported glossitic changes in 11 of 65 cases. The tongue is commonly quite painful and sensitive.¹⁴ Jones and Owen¹⁵ described the smooth, glazed tongue as devoid of all papillae or with irregular islands of persisting epithelium. Witts¹⁶ noted the close similarity of the glossitic changes in this condition to those of pernicious anemia, but expressed the opinion that apthae and circular areas of denudation were more common in the Plummer-Vinson syndrome. Witts likewise reported the tendency for the lingual

changes to undergo a complete remission *pari passu* with the general improvement. Occasionally a residual island of atrophy may persist. While achlorhydria is the rule, the administration of diluted hydrochloric acid apparently has no beneficial effect.¹⁶ Liver, also, is without specific action. The anemia responds most readily to transfusions, and iron is commonly effective as in Case IV.

The streptococcus was adjudged the responsible etiologic agent in the glossitis of pernicious anemia by Hunter,² Schneider and Carey¹⁷ isolated the streptococcus viridans in cultures from the deeper layers of the tongue and demonstrated this organism deep in the muscles of the tongues of pernicious anemia patients studied by biopsy. The scope of the present discussion does not admit of a consideration of the probable significance of this finding, but the overwhelming weight of evidence favors the contention that the streptococcal invasion of the tongue is incidental rather than causal in pernicious anemia. A rather striking example of streptococcal glossitis is cited in Case V, because of the etiologic problem it suggests.

Case V Miss J. J., a white nurse aged 40 years, complained of a sore mouth. For three years the gums and tongue have been almost continuously sore. Since the age of 16 years the patient has been periodically troubled with canker-sores on the gums, buccal mucous membranes and tongue. Lately the lips have become dry and sore. Occasionally a vaginal discomfort, likened to that of a canker sore, has been remarked by the patient. Unexplained subcutaneous hemorrhages have occurred in two fingers in the past nine months. For seven or eight years recurrent swelling of the right upper eyelid has developed at irregular intervals. Fatty foods were not well tolerated. Citrus fruits and tomatoes were avoided because

of the discomfort which they induced locally in the mouth. The mouth was the chief seat of pathologic findings to physical examination. The mucous membrane of the entire mouth and oropharynx was deeply injected and sensitive. The tongue was beefy with especial congestion at the tip and edges. Transverse furrows were apparent over its dorsum and the papillae were quite atrophic. Sublingual soreness and boggyness were observed. The gustatory sense for sour and bitter was lost, but sweet was promptly perceived. The hemoglobin was 75 per cent and erythrocytes 46 million. Free hydrochloric acid appeared in the gastric contents only after histamine. Repeated cultures of the tongue scrapings showed streptococci in overwhelming predominance. Sensitization tests for food, keratinoids and streptococci proved negative.

Nor do these examples exhaust the clinical conditions which are attended by the atrophic tongue. Probably the tongue of sprue most closely approximates that of pernicious anemia. Manson-Bahr and Willoughby¹⁸ gave a comprehensive consideration to this detail. The earliest manifestation in their experience was an increased sensitiveness to hot fluids, spices and tobacco smoke followed by a perversion to salt and to sweets. The fungiform papillae were seen to stand out prominently toward the tip of the tongue as hyperemic dots. Aphthous ulceration of the buccal mucous membrane and tongue occurred on the rupture of tiny vesicles in their deeper layers. These aphthae induced marked tenderness and sensitiveness in the parts affected, especially the inner margin of the lower lip, the frenum, tip and sides of the tongue and less commonly the mucosa of the cheek opposite the lower molars. The chronic sprue tongue was smooth and polished. In their judgment while the oral symptoms may recur or persist

after the gastro-intestinal situation has been controlled, "it is a useful guide to consider a patient with obvious tenderness of the mucosa of the mouth and with unrestored function of the filiform and fungiform papillae as incompletely restored to health. The tongue and mouth should constitute an index of what is going on in the rest of the alimentary tract."

In pellagra, ulceration of the tongue is not uncommon along its edges. This ulceration may eventually lead to a complete denudation and the tongue assume a beefy redness. At this period mastication may be extremely painful and deglutition a torture. Again, widespread ulceration may be unattended by serious distress. The latter circumstance doubtless arises from the mental deterioration of the pellagrin in many instances. The deeper injection and the firm, sharp contour of the pellagrous tongue are in contrast to the moderately congested and flabby tongue of sprue. Denudation rather than atrophy accounts for the smooth tongue in pellagra. The response of the glossitic manifestations to proper dietetic management is one of the earliest measures of its success.

The anemias of pregnancy and the puerperium are frequently attended by soreness and atrophy of the tongue.¹⁹ As a matter of fact the early descriptions of pernicious anemia attended by atrophy of the tongue were in several instances^{20, 21} classical examples of the anemia of pregnancy. Keefer and Yang²² observed glossitis with atrophy in malnutrition attended by dysentery and anemia. Relief of the underlying condition resulted in a return of normal papillae. Lewis²³ noted glossitis with low papillae in a case of

pyloroplasty complicated by peritonitis and obstruction for which a jejunostomy had been performed. Meulengracht²⁴ reported atrophy of the lingual papillae with injection and blebs succeeding intestinal stricture, in a review of the blood changes attendant upon this condition. Isaacs, Sturgis and Smith⁴ noted the tongue in *dibothriocephalus latus* infestation to be smoother than normal but not atrophic. Glossitis with atrophy of the tongue has been observed in achlorhydria by Schneider and Carey²⁵ among others. Wilkinson and Oliver,²⁶ for example, found a sore tongue or an ulcerative stomatitis the outstanding feature in 25 of 53 cases with achlorhydria. Oatway and Middleton³ found a definite correlation between gastric anacidity and lingual atrophy. Witts¹¹ admitted the common coincidence of achlorhydria and glossitis, but pointed out the occurrence of the latter in certain cases of anemia and malnutrition in which the free hydrochloric acid of the gastric contents was normal.

From this review it may be concluded that glossitis with ultimate atrophy occurs in a considerable group of conditions. It is beside the purpose of this presentation to hypothesize as to the possible significance of this circumstance. Lewis²³ in a comprehensive survey of the subject, concluded that "there is no general agreement as to the cause of lingual atrophy in any of the conditions considered", although he clearly leaned toward a conditioned deficiency as the background. Castle and his fellow-workers²⁷ advanced further evidence in support of this position. Whatever the final answer to this question may be, the clinical significance of these lingual changes,

both in the diagnosis and the prognosis of the conditions discussed, must not be overlooked To this end the ad-

vantage of serial tongue prints as a means of studying the progress of the glossitic process is strongly urged

REFERENCES

- ¹DAWSON, J Thoughts on the tongue as an element in diagnosis, *West Jr Med and Surg*, 1846, vi(n s), 277-298
- ²HUNTER, W Severest anaemias, their infective nature, diagnosis and treatment, 1909, Macmillan & Co, London, 1, 114
- ³OATWAY, W H, Jr, and MIDDLETON, W S The correlation of lingual changes with other clinical data, *Arch Int Med*, 1932, xlix, 860-876
- ⁴ISAACS, R, STURGIS, C C, and SMITH, M Tapeworm anemia, *Arch Int Med*, 1928, xlii, 313-321
- ⁵MINOT, G W, and MURPHY, W P A diet rich in liver in the treatment of pernicious anemia, study of 105 cases, *Jr Am Med Assoc*, 1927, lxxxix, 759-766
- ⁶ISAACS, R Systemic relapses during liver induced hematopoietic remissions in pernicious anemia, *Am Jr Med Sci*, 1928, clxxviii, 500-505
- ⁷ISAACS, R, STURGIS, C C, and SMITH, M Treatment of pernicious anemia, *Jr Am Med Assoc*, 1928, xci, 1687-1690
- ⁸KAZNELSON, P, REIMANN, F, and WEINER, W Achylische Chloranämia, *Klin Wchnschr*, 1929, viii, 1071-1074
- ⁹WATKINS, C H A classification of chronic idiopathic secondary anemia, *Jr Am Med Assoc*, 1929, xciii, 1365-1367
- ¹⁰WITTS, L J Simple achlorhydric anemia, *Guy's Hosp Rep*, 1930, lxxx, 253-296
- ¹¹WITTS, L J Chronic microcytic anemia, *Brit Med Jr*, 1931, ii, 883-888
- ¹²VINSON, P P Hysterical dysphagia, *Minn Med*, 1922, v, 107-108
- ¹³MOERSCH, H J, and CONNER, H M Hysterical dysphagia, *Arch Otolaryng*, 1926, iv, 112-119
- ¹⁴HURST, A F The Plummer-Vinson syndrome (spasm of the pharyngo-esophageal sphincter with anemia and splen-
- omegaly), *Guy's Hosp Rep*, 1926, lxxxi, 426-428
- ¹⁵JONES, A M, and OWEN, R D Dysphagia associated with anemia, *Brit. Med Jr*, 1928, i, 256-257
- ¹⁶WITTS, L J The syndrome of glossitis, dysphagia and anemia, *Guy's Hosp Rep*, 1931, lxxxii, 193-204
- ¹⁷SCHNEIDER, J P, and CAREY, J B The nature of the glossitis in pernicious anemia, *Minn Med*, 1927, x, 214-222
- ¹⁸MANSON-BAHR, P, and WILLOUGHBY, H Studies on sprue with special reference to treatment, based upon analysis of 200 cases, *Quart Jr Med*, 1930, xxiii, 411-442
- ¹⁹LARRABEE, R C The severe anemia of pregnancy and the puerperium, *Am Jr Med Sci*, 1925, clxx, 371-389
- ²⁰BARCLAY *Med Times*, 1851, 480 (Quoted by Hunter, Ref 2)
- ²¹MULLER, H Die progressive perniciose Anämie nach Beobachtungen auf der medicinischen Klinik in Zurich, 1877, C Schmidt, Zurich
- ²²KEEFER, C S, and YANG, C S Anemia of undernutrition, *Natl Med Jr China*, 1929, xv, 701-720
- ²³LEWIS, G E The smooth tongue, a study of deficiency disease, *Practitioner*, 1930, cxxv, 749-755
- ²⁴MEULENGRACHT, E Pernicious anemia in intestinal stricture (with one liver-treated case), *Acta med. Scandinav*, 1929, lxxii, 231-240
- ²⁵SCHNEIDER, J P, and CAREY, J B The clinical significance of primary achlorhydria, *Jr Am Med Assoc*, 1928, xci, 1763-1768
- ²⁶WILKINSON, J F, and OLIVER, T H Some clinical conditions associated with achlorhydria, *Lancet*, 1931, i, 66-71
- ²⁷CASTLE, W B, HEATH, C W, STRICKLAND, M B, and TOWNSHIP, W C The relationship of disorders of the digestive tract to anemia, *Jr Am Med Assoc*, 1931, xciii, 904-907

The Significance of Fever and Blood Protein Changes in Regard to Defense Against Infection

By

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FEVER, one of the most constant and striking features characteristic of the invasion and growth of pathogenic microorganisms, has attracted the attention of physicians since the beginning of medicine. Hippocrates, Celsus, Sydenham and many others considered it of importance as a defensive mechanism against disease, "*vis medicatrix naturae*." This viewpoint prevailed generally until the nineteenth century when a number of observers took an opposite stand. Claude Bernard, Liebermeister and others devoted much attention to fever and believed it to be harmful. Their opinion in regard to the deleterious effect of fever on the body appeared to be greatly enhanced by the contemporary development of cellular pathology and the demonstration of "cloudy swelling" as a result of fever by Virchow. Their publications were widely accepted and led to the adoption of various measures for the purpose of reducing fever. Naunyn was one of the first to attack Liebermeister's teaching, and showed that fever

in itself was not responsible for the various pathological changes often found in febrile diseases, but that the damage was caused primarily by the invading organisms. It was admitted that extremely high or prolonged fever, as for instance in heat stroke, often produces pathological changes in tissues.

Recent clinical and experimental studies also show that excessively high body temperatures, induced artificially, are harmful and may prove fatal.

Controversy in regard to the harmful or beneficial effects of fever reached its height late in the nineteenth century. The weight of evidence now appears to favor the latter contention. Experiments designed to show the beneficial influence of fever as a defense mechanism against bacterial infection may be divided into four classes,—the demonstration of (a) antibacterial and antitoxic effects of fever temperature *in vitro*, (b) the enhancement of antibacterial and antitoxic ability of the host by raising the body temperature, (c) the diminished resistance of the host to bacterial infection by lowering the body temperature, and (d) the beneficial effects of intercurrent infection and fever on other diseases.

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As early as 1876 Heydenreich¹ noted that the spirilla of relapsing fever lost motility sooner at 40° C than at normal body temperature. Many other studies later showed that bacterial growth appears to be inhibited by temperatures over 40° C.^{2, 3} Yoshioka⁴ showed that pneumococci, when grown at 39° C, lost both virulence and specificity. Vibriolysin and tetanolysin were destroyed by heat *in vitro*, and guinea pigs heated by light treatment were more resistant to these toxins than unheated animals, according to experiments of Sonne.⁵

Filehne, Chienisse, Walter¹ and Trudeau showed that animals kept warm or heated were less susceptible to experimental infection than those whose temperature was lowered. Recently, Robertson,⁶ in observations on experimental pneumonia in dogs, noted that when morphine was given in quantities sufficient to produce a well marked depression of body temperature, subsequent infection with pneumococcus resulted in a severe, prolonged and widespread infection often accompanied by bacteremia and ending in death. The same quantities of pneumococci in unmorphinized dogs produced a mild localized disease lasting two or three days. Rolly and Meltzer,⁷ in 1908, showed that heated animals were more resistant to bacterial infection than unheated ones but were unable to demonstrate any special bactericidal substance in the blood, nor was there a constant degree of phagocytosis demonstrable in the heated animals. In other experiments they showed that phagocytosis became more active as the temperature exceeded 37° C until 40° was reached.

Temperature higher than 40° C interfered with phagocytosis.

Rolly and Meltzer,⁷ Ludke,² Friedberger and Bettac⁸ and others demonstrated an increase of agglutinins and hemolytic amboceptor by heating animals. The increase in titer of typhoid bacillus agglutinins as a result of fever due to other causes has been repeatedly observed both clinically and experimentally. The fact that chronic diseases are occasionally favorably influenced by intercurrent acute infection has been known for many years and has led to the common usage of hot baths and heliotherapy, which were already used by the ancients. In modern times, the inoculation of malaria or relapsing fever parasites, the injection of foreign protein or the use of diathermy are widely employed for the purpose of inducing therapeutic fever.

A new approach to studies on the effects of infection and fever has been furnished by observations in regard to the suspension stability of the blood. This phenomenon although widely observed for many years, then disregarded, was restudied and popularized by Fåhræus⁹ in 1921. Since then, hundreds of papers have appeared concerning studies of the suspension stability of the blood expressed as sedimentation time or speed of erythrocytes, in many diverse conditions.

Fever and a disturbance of the suspension stability of the blood may occur independently but usually occur together and accompany most if not all infectious diseases. The decrease of suspension stability was shown to be due to an increase of the globulin and fibrinogen content of the blood.

which occurs in most febrile infectious diseases and in certain afebrile conditions as in pregnancy and myeloma³⁸ Whether fever alone is responsible for the increase of blood protein or whether it is due to effects of the invading organism has not been decided Fåhræus believed it to be due chiefly to the effects of the virus Experiments by Frisch and Starlinger,¹¹ Puxeddo¹² and others, and studies in our own laboratory also indicate that fever alone, as induced by diathermy is not effective in causing marked increases in either globulin or fibrinogen³⁹ It is probable that a combination of factors in febrile infectious disease operates to produce plasma protein changes by stimulating globulin or fibrinogen producing organs, presumably the bone marrow or the endothelial system

With increase in the globulins, there occurs an increase in the viscosity of the plasma Then, as a result of an alteration of electrical charges¹⁰ the erythrocytes clump and settle rapidly In attempting to show the beneficial effects of a decrease in the suspension stability of the blood in regard to defense against infection, Fåhræus¹⁰ has shown that a slowing of the blood stream such as occurs in inflammatory tissue, permits the erythrocytes to form large clumps and as such they tend to occupy the axial current of the slowly moving stream according to physical principles As a result, leucocytes are crowded out and forced along the walls of the vessels to a favorable position for migration through the vessel wall into the area of inflammation (See Zinsser,¹³ p 300)

In returning to the subject of the aggregation of erythrocytes in plasma of increased viscosity, the question arises as to whether other suspended particles may not be similarly affected Leucocytes may be clumped¹⁴ but little attention has been given to the effects of plasma changes on bacteria^{15,16} Both erythrocytes and bacteria are known to carry negative electrical charges¹⁷ so that if erythrocytes tend to clump when the electrical equilibrium is disturbed by a change of plasma proteins, bacteria theoretically should be similarly affected If it can be shown that the changes in the plasma which accompany febrile infectious diseases favor the clumping of bacteria, another point will be added in favor of fever and plasma protein changes as mechanisms of defense against infection Bull,¹⁸ Rich,¹⁹ Cannon^{20, 21} and others have shown that the agglutination of bacteria is one of the most important steps in the recovery from experimental infection

EXPERIMENTAL

The following experiments were performed to determine the effect of changes of viscosity of the plasma and of other fluids on the clumping of bacteria

Several preliminary experiments were made to test the behavior of various kinds of bacteria when suspended in samples of plasma of varying viscosity Type II pneumococci, typhoid bacilli and Friedlander bacilli were suspended in plasma obtained from a normal individual and in plasma obtained from a patient suffering from lobar pneumonia due to type I

pneumococcus The viscosity of the normal plasma diluted 1 in 10 with 10 per cent solution of sodium citrate was 17 (Hess viscosimeter) and the suspension stability was such that the sedimentation time of erythrocytes, measured from the time the level of the red cell column dropped to the 60 mark on a tuberculin syringe, was over two hours The viscosity of the patient's plasma was 24 and the sedimentation time 10 minutes There was little or no perceptible effect on the bacteria when suspended in the plasma of higher viscosity than normal In some instances, there was a slight tendency to clump in the more viscid plasma

Very different results were obtained when minute amounts of specific immune serum were added to the plasma Tests were made by using immune serum obtained from a patient vaccinated with typhoid-paratyphoid A and B vaccine and paratyphoid B bacilli Instead of preparing dilutions of specific immune serum in normal physiologic salt solution as customary, dilutions were made in parallel in normal plasma and in plasma of increased viscosity When bacilli were suspended in the dilutions as arranged, clumping occurred in a far higher titer (1-10240) in the high viscosity plasma than in normal plasma (1-320)

Similar results were obtained when the viscosity of normal plasma was increased by the addition of gum acacia, as shown in table 1

The agglutination reaction shown in table 1 indicates that increase in viscosity enhances the specific agglutination effect of specific immune serum²² Results similar to these were obtained in experiments with type I pneumococci and type I antipneumococcus serum, and with type b Friedlander bacilli which agglutinate specifically in type II antipneumococcus serum

When smears stained with Wright stain were made from each tube and examined, microscopic clumping was found to occur within 10 minutes at 37° C Bacteria suspended in plasma of high viscosity or in plasma to which acacia had been added stained with difficulty They appeared pale and swollen or as if thickly coated with a gummy substance which prevented penetration of the dye Capsules of pneumococci and Friedlander bacilli were often accentuated In many preparations it appeared as if most of the organisms had vanished Resuspension or washing the organisms in physiological salt solution restored the normal staining reaction In most microscopic preparations made from suspensions of bacteria in colloidal solutions, bacteria appeared to be en-

TABLE 1

DILUTIONS OF SPECIFIC IMMUNE SERUM	40	80	160	320	640	1280	2560	5120	10240	20480	Control
Plasma + 2½% acacia	+++	+++	+++	+++	+++	++	—	+	—	+	—
Normal plasma	++	+	+	+	—	—	—	—	—	—	—

Microscopic agglutination of *Bacillus paratyphosus* B in specific immune serum diluted with high viscosity plasma (upper row) and with normal plasma (lower row) Reading made after 2 hours incubation at 37° C

meshed, even if not specifically clumped, in amorphous patches of lightly stained material presumably of the colloid itself. Bacteria suspended in plain broth or in salt solution were always diffusely scattered. Typhoid bacilli immediately became non-motile when suspended in 5 per cent solutions of gum acacia.

Increase in viscosity, as such, is apparently not alone responsible for the reactions described. Further experiments showed that solutions of other viscous substances—gum tragacanth, agar, egg white, starch paste, gelatin and glycerin adjusted to similar viscosity were less effective than gum acacia in enhancing specific agglutination.

Experiments with blood from a case of hyperinosis. Plasma obtained from a patient with myelomata contained 5.48 gm of fibrinogen and 2.27 gm euglobulin per 100 c.c.²³ The plasma viscosity was 7 as compared with 1.8, the viscosity of normal plasma, according to the technic used. The sedimentation

time was 5 minutes. Two dilutions, one of 1-100 and one of 1-200, of type I antipneumococcus serum were prepared with the whole blood of high viscosity and with normal blood as a control. Specific antipneumococcus serum seldom causes clumping in dilution as high as 1 to 200 when tested by the usual methods. Type I pneumococci were added to each tube. Stained preparations were made after 10 minutes incubation at 37° C.

Large clumps of pneumococci were found in preparations from the high viscosity blood in both dilutions of antipneumococcus serum. The leucocytes and platelets were not involved in the agglutination process and appeared to take no part in the reaction which is in harmony with the observations of Wright³ and others. Pneumococci were diffusely scattered in the smears made from both tubes containing normal blood and immune serum. An illustration of the type of clumping referred to is shown in figure 1.



FIG. 1. Type I pneumococci and type 1 antipneumococcus serum 1-200, incubated 10 minutes with (A) normal blood (B) high viscosity blood. Pneumococci are clumped in high viscosity blood with a minute amount of specific immune serum.

Similar results were obtained when the plasma of this patient and normal plasma were used with type II antipneumococcus serum and type b Friedlander bacilli. Clumping of bacilli occurred in dilutions of immune serum as high as 1-160 in the high viscosity plasma but only in the strongest concentration (1-10) in the normal plasma. An illustration of the clumping reaction is shown in figure 2.

were incubated for two hours. At this time stained preparations were made from the contents of each tube. The tubes were then kept in the icebox over night and read for macroscopic agglutination. The results of macroscopic agglutination are shown in table 2.

It is evident from the table that within a certain range, viscosity due to gum acacia has a striking effect on the



FIG 2 Type b Friedlander bacilli and type II antipneumococcus serum 1-40, incubated with, (A) normal plasma, (B) plasma of high viscosity. Bacilli are clumped in high viscosity plasma with a minute amount of specific immune serum.

Effect of varying grades of viscosity. Tests were made to determine the effect of varying degrees of viscosity with varying concentrations of specific immune serum. The experiment was arranged as shown in table 2. A solution of gum acacia was diluted in physiological saline solution so that varying degrees of viscosity were obtained. To the series of tubes containing these dilutions, type I antipneumococcus serum was added in the dilutions indicated. Heat-killed type I pneumococci were added and the tubes

sensitivity of specific agglutinins. Increase of viscosity beyond 5.6 tends to inhibit clumping. It is of interest to note that the range of viscosity at which clumping occurs best is close to the range of the viscosity of blood during certain infectious diseases.²⁴ The macroscopic results described checked with the microscopic examination of the clumping reaction made after two hours incubation. Identical results were obtained when type II antipneumococcus serum and type b Friedlander bacilli were used.

TABLE 2

DILUTIONS OF TYPE I ANTI- PNEUMOCOCCUS SERUM		1-10	1-20	1-40	1-80	1-160	1-320	1-640	1-1280	1-2560	1-5120	Control
Salt solution		++++	++++	++++	++	—	—	—	—	—	—	—
16 ++		++++	++++	++++	++	+	—	—	—	—	—	—
22 ++		++++	++++	++++	+++	++	+	—	—	—	—	—
35 ++		++++	++++	++++	++++	++	++	++	++	+	—	—
56 ++		++	++	++	++	+	+	+	+	+	—	—
8 +		+	+	+	+	+	+	+	—	—	—	—
11 +		+	+	—	—	—	—	—	—	—	—	—
++++	disc formation											
+++	disc easily broken up											
++	coarse clumping											
+	fine clumping											
—	no clumping											

The effect of varying degrees of viscosity on the clumping of type I pneumococci in varying concentrations of specific immune serum Viscosity from 3.5 to 8 appears to exert the maximum effect

Effect of changes of viscosity in vivo Mice were inoculated intraperitoneally with 0.5 c.c. of an 18 hour broth culture of type I pneumococci and divided into three groups. One group was injected intraperitoneally with 0.1 c.c. of type I antipneumococcus serum diluted in 0.5 c.c. of normal physiological saline solution, the second group with 0.5 c.c. of a 10 per cent solution of gum acacia and the third group with 0.1 c.c. of serum diluted in 0.5 c.c. of 10 per cent acacia. The injections were arranged so that all mice received similar quantities of fluid intraperitoneally. Mice from each group were killed after 15, 30 and 60 minutes. Stained films were made from the peritoneal fluid of each mouse.

Results In mice receiving the minute amount of immune serum, pneumococci were found in great numbers diffusely scattered. The leucocytes were free and scattered. In mice injected with acacia alone, pneumococci stained poorly and many were scarcely visible, but no clumping was observed. Clumping of leucocytes was the most prominent feature. The most striking results were found in mice receiving both serum and acacia. Even at the end of 15 minutes most of the pneumococci had become invisible or had disappeared. A few tight clumps appeared here and there, either free, or attached to, or included in, agglomerations of leucocytes. Phagocytosis was slight. Leucocytes free in the peritoneal cavity appeared to take part in the clumping reaction, in contrast to their behavior in the blood. An illustration of the results obtained is shown in figure 3.

Discussion The non-specific effect of blood colloids on specific agglutination was observed by Bordet and Streng in 1909^{25, 26}. The agglutinative effect of the colloid was called conglutination and was recognized as distinct from the effects of specific agglutination. By adding ox serum Streng obtained a marked clumping of bacteria in dilutions of specific antisera which were too weak to cause agglutination unaided. He and Barikine²⁷ showed that conglutinin was removed by precipitating the globulin fraction of the serum. Dean²⁸ in 1911 reported similar observations and again showed that agglutinating serum contains two factors both of which are necessary to cause clumping, the one is a specific antibody, the other a non-specific substance which is possibly globulin. He also showed that a deficiency of the non-specific substance could be made up by the addition of globulin.

The experiments reported in this paper also show that at least two factors play a rôle in clumping of suspended organisms and that specific agglutination is influenced by various colloidal substances.

The mechanism involved in the agglutination or clumping of bacteria has received much attention. Gruber²⁹ in 1896 was the first to show that increased viscosity of bacteria caused them to adhere to one another and favored their subsequent englobement by phagocytes. The physicochemical principles involved in the clumping reaction have been studied by many observers. (See Northrop³⁰ and Zinner³¹ for references and discussion.) The outcome of much experimental

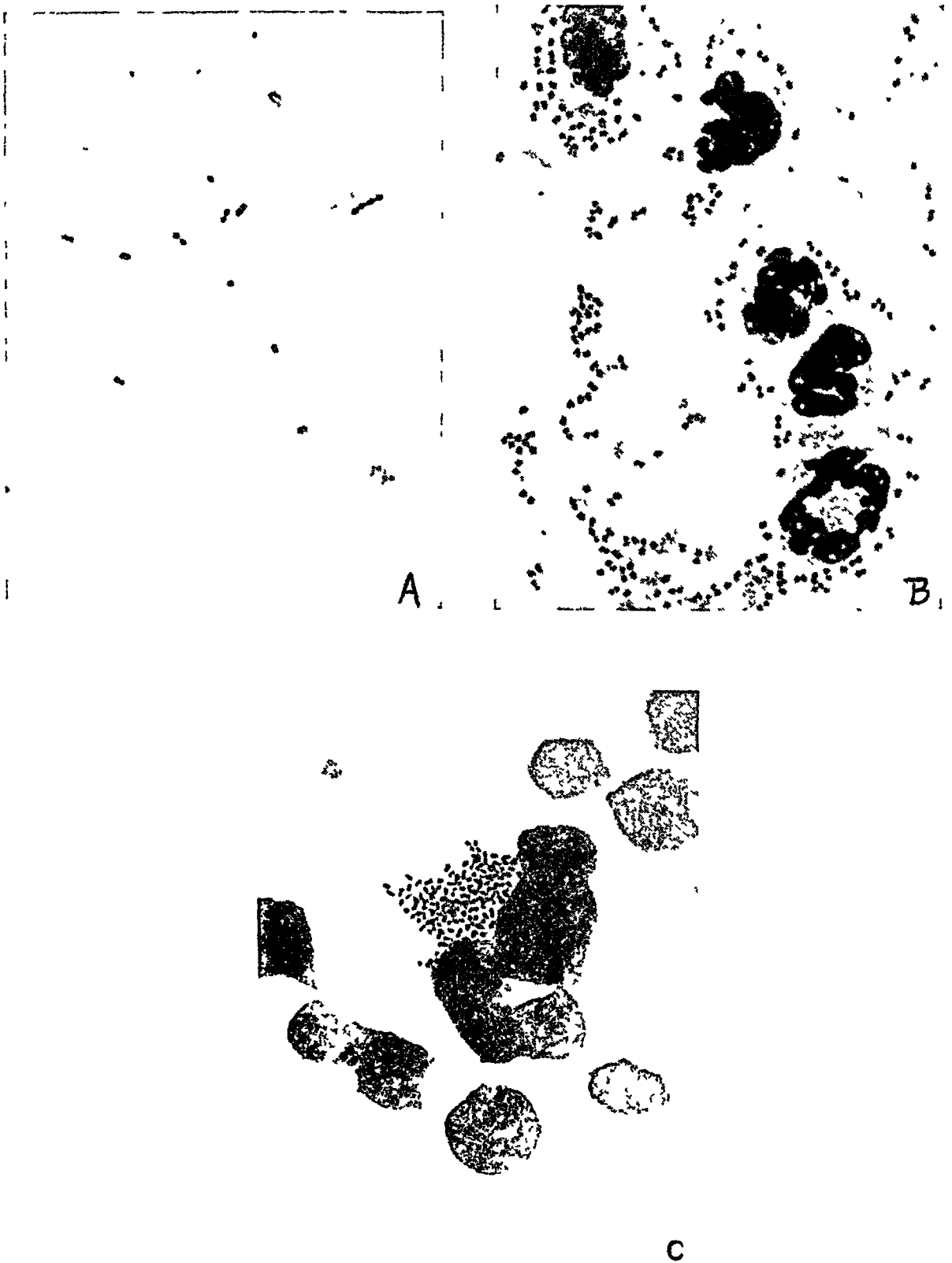


FIG 3 Effect of viscosity on agglutination of type I pneumococci *in vivo* (A) serum from mouse injected intraperitoneally with type I antipneumococcus serum, (B) from a mouse injected with 10 per cent gum acacia solution, (C) from a mouse injected with both serum and acacia. In A and B the organisms are diffusely scattered. In B the leucocytes tend to clump and in C both pneumococci and leucocytes clump.

work indicates the complexity of the phenomenon. Bacteria in suspension appear to behave much like other protein particles. Their agglutination and precipitation depends largely upon repulsive and cohesive forces. Changes in the composition of the menstuum in which bacteria are suspended alter the cell surfaces, bring about changes in electrical charge and cause clumping.

The experiments reported in this paper concern the enhancement of specific agglutination brought about by changes in the plasma proteins as a result of febrile infections. The reaction was shown to be influenced by increase in the globulin-fibrinogen content of the blood which increased the viscosity of the plasma. The effects of increase of viscosity of the plasma could be reproduced by increasing the viscosity by adding other colloids, especially gum acacia, to the suspension. The effects were observed both *in vitro* and *in vivo*.

Increase of fibrinogen or globulin in the blood occurs in almost all infections, but whether fever in itself is directly responsible for plasma protein changes or whether these changes merely accompany fever and both are caused by substances liberated by the virus is as yet uncertain. It appears that plasma protein changes result from the stimulation or irritation of globulin- or fibrinogen-forming organs and commonly occur in afebrile conditions (pregnancy myeloma) as well. Studies by Lloyd and Paul³¹ indicate that fever alone does not produce plasma protein changes but that the effect is dependent upon the intensity of the infection. It has been shown also that elevation of the body temperature by

diathermy produced but slight and transient blood protein changes.³¹ On the other hand, marked changes are caused promptly within two or three hours by the parenteral injection of protein and non-protein substances.³² The indications are, therefore, that both fever and plasma protein changes may occur independently and are due to the effects of the virus. Studies of these factors are under way in our laboratory at present.

At any rate, I have attempted to show that the changes in the blood proteins and increase of blood viscosity which occur during infectious diseases may represent an important mechanism in the defense of the body against infection. A number of observers^{18, 19, 20} have shown that agglutination is an important factor in the defense mechanism of the host. Mudd^{33, 34} and his associates have shown that increase of cohesiveness closely parallels increase in phagocytosis. It has been shown in this study that the optimal degree of viscosity produced artificially *in vitro* closely approximates the degree of viscosity of plasma found to exist during infectious disease and that this viscosity favors agglutination of bacteria. Whether these changes are of teleological significance is difficult to say. The effects discussed are non-specific and mechanical in nature. The fact that increases of blood colloids appear to prepare bacteria for clumping and ultimate phagocytosis permits one to regard the phenomenon in the nature of an opsonin.

Certain instances at first appear to contradict the suggestion that increase of viscosity due to increase of blood globulin is an important factor in de-

fense against infection. It is known that diseases like kala-azar and leukemia, are peculiar in that they are accompanied by marked increase of the plasma proteins, yet they particularly predispose the patient to secondary infection. It has been shown,³⁵ however, that in the diseases mentioned there appears to be an inability to elaborate specific antibodies. The data presented in this paper indicate that increases in viscosity in the absence of specific immune bodies are without effect. A further and more contradictory example pertains to the fatal infection from avirulent R pneumococci in horses used for the production of antipneumococcus serum.³⁶ In this instance, horses whose blood is known to be exceptionally high in fibrinogen content had been highly immunized by the intravenous injection of living S pneumococci, yet in the presence of high specific immunity and high fibrinogen content of the plasma, they succumbed to infection.

Other evidence of the effect of increase of viscosity on specific agglutination has developed from an entirely different approach. Fitch, Donham, Bishop and Boyd³⁷ have shown that the presence of agar greatly enhances the specific agglutination of organisms of the Brucella group. They have applied the phenomenon to practical purposes in agglutination tests.

The demonstration of the increase of the effective range of agglutination by specific immune serum by increasing the viscosity of the menstruum raises a number of questions for future investigation. One pertains to the apparent non-specific reactivation of agglutinins during infectious disease, as for example, the reappearance

of typhoid agglutinins during other infections. During and after lobar pneumonia, to what extent does the increase of the agglutination titer of the patient's blood depend upon the strength of the specific immune bodies or merely upon the increase of the globulin or fibrinogen? A relationship between the suspension stability of the blood and the titer of specific typhoid agglutinins has already been noted by Vorschütz^{15b} and others. Finally what are the potentialities of increasing therapeutic effectiveness of specific immune serum by increasing the viscosity of the plasma by dietary or other measures?

SUMMARY

Evidence has been presented by many observers to show that fever exerts a beneficial influence in the defense mechanism against infection. It has been shown that temperature at fever levels tends to influence the growth of bacteria adversely, to diminish the potency of toxins, to favor phagocytosis and to stimulate the development of immune bodies.

In experiments reported in this paper it has been shown that the increased viscosity of the plasma which occurs during febrile infection as a result of increase of certain plasma proteins enhances the specific agglutination power of specific immune serum. Other investigators have shown that agglutination is an important factor in the restriction of bacterial growth and spread in the tissues. It is therefore suggested that the plasma protein changes which occur during infectious disease and enhance agglutination are important factors in the defense mechanism against infection.

REFERENCES

- ¹Cited by Ludke
- ²LUDKE, H D Über die Bedeutung der Temperatursteigerung für die Antikörperproduktion, *Deutsch Arch klin Med*, 1909, xcv, 425-456
- ³WRIGHT, H D Experimental pneumococcal septicemia and antipneumococcal immunity, *Jr Path and Bact*, 1927, xxx, 185-252
- ⁴YOSHIOKA, M Veränderungen der Agglutination bei Pneumokokken, *Ztschr Hyg u Infectiöskr*, 1923, xcvi, 232-243
- ⁵SONNE, C Investigations on guinea-pigs relating to the influence of the light bath on the action of diphtheria toxin, *Acta Med Scand*, 1922, lvi, 619-628
- ⁶ROBERTSON, O H Personal communication
- ⁷ROLLY and MELTZER Experimentelle Untersuchungen über die Bedeutung der Hyperthermie, *Deutsch Arch klin Med*, 1908, xciv, 335-364
- ⁸FRIEDBERGER, E, and BETTAC, E Über den Einfluss der Fieberstiche auf normale Ambozeptoren und das Komplement beim Kaninchen, *Ztsch f Immun*, 1912, xii, 29-64
- ⁹FAHRAEUS, R The suspension stability of the blood, *Acta Med Scand*, 1921, lv, 1-180
- ¹⁰FAHRAEUS, R The suspension stability of the blood, *Phys Rev*, 1929, ix, 241-274
- ¹¹FRISCH, A, and STARLINGER, W Chemisch-physikalische Blutuntersuchungen zur Frage der Protoplasmaaktivierung, *Ztsch f d ges Exper Med*, 1921, xxiv, 142-158
- ¹²PUXEDDO Influenza della diatermia sulla V S degli eritrociti, *Ref Ber über d ges Physiol*, 1925, xxvii, 82
- ¹³ZINSSER, H Resistance to infectious diseases, The Macmillan Co, New York, 1931, p 244
- ¹⁴SCHILLING, V, and SCHULTZ, E Die Senkungsgeschwindigkeit der Leukocyten, ihre Abhängigkeit von deren Agglutinationsgrade und ihre Unabhängigkeit von der Suspensionstabilität der Erythrocyten, *Klin Woch*, 1923, No 48, 2198-2201
- ¹⁵VORSCHUTZ, J (a) Untersuchungen über Agglutination und Sedimentierung von Bakterien, *Arch f d ges Phys*, 1921, clxxxvi, 290-295, (b) Beruht die Impf-Gruber-Widal Reaktion auf denselben physiko-chemischen Momenten wie die unspezifische und geht erstere ebenso parallel der Senkungsgeschwindigkeit der Erythrocyten wie letztere, *Centr Bakt*, 1923, xc, 105-109
- ¹⁶MANDELSTAMM, A Zur Frage über die Beziehungen zwischen Blutkorpersenkungsgeschwindigkeit und Bakterienagglutination, *Monatsch f Geburtsh*, 1925, lxx, 180-189
- ¹⁷NORTHROP, J H, and DEKRUUF, P H The stability of bacterial suspensions, II and III, *Jr Gen Phys*, 1921-22, IV, 639-667
- ¹⁸BULL, C G The mechanism of the curative action of antipneumococcus serum, *Jr Exper Med*, 1915, xlii, 457-465, 475-483, Further observations on the agglutination of bacteria in vivo, *Jr Exper Med*, 1916, xxiv, 7-33
- ¹⁹RICH, A R *Proc Nat Acad Sci*, 1930, xvi, 460-463
- ²⁰CANNON, P R, and PACHFEO, G A Studies in tissue immunity, *Arch Path* 1930, vi, 749-765
- ²¹CANNON, P R, SULLIVAN, F L, and NECKERMANN, L F Conditions influencing the disappearance of living bacteria from the blood stream, *Jr Exper Med*, 1932, lx, 121-137
- ²²REIMANN, H A Possible significance of decreased suspension stability of the blood, *Science*, 1931, lxxii, 513
- ²³REIMANN, H A Effect of viscosity on specific agglutination, *Proc Soc Exper Biol and Med*, 1932, xlii, 565
- ²⁴BACHMANN, E Die klinische Verwertung der Viskositätsbestimmung, *Deutsch Arch f klin Med*, 1908, xcii, 400-425
- ²⁵BORDET J, and STENG, O Les phénomènes d'absorption et la coagulation du serum de boeuf, *Centralbl Bakt*, 1909, xlii, 260-288
- ²⁶STENG, O Studien über das Verhalten des Rinderserums gegenüber der Miltobakterien, *Centralbl Bakt*, 1909, l, 47-78

- ²⁷BARIKINE, W Contribution à l'étude sur la congulation du précipité spécifique, *Centralbl Bakt*, 1910, lvi, 150-160
- ²⁸DEAN, H R On the factors concerned in agglutination, *Proc Royal Soc London*, 1912, lxxxiv, Series B, 416-434
- ²⁹GRUBER, M Über active und passive Immunität gegen Cholera und Typhus, sowie über die bacteriologische Diagnose der Cholera und des Typhus, *Wien klin Wchnschr*, 1896, ix, 204-209
- ³⁰NORTHROP, J H New knowledge of bacteriology and immunology, *Jordan and Falk, Univ Chicago Press*, 1928, 782
- ³¹LOYD, R B, and PAUL, S N Serum protein changes in malaria and typhoid fever, *Indian Jr Med Res*, 1929, xvii, 583-610
- ³²LOHR, H Die Beeinflussung der Blutkorpersenkungsgeschwindigkeit durch Reizstoffe, *Ztschr f d ges Exper. Med*, 1922, xxvii, 1-13
- ³³MUDD, S, LUCKÉ, B, McCUTCHEON, M, and STRUMIA, M On the mechanism of opsonin and bacteriotropin action, *Jr Exper Med*, 1929, xlix, 779-797
- ³⁴LUCKÉ, B, McCUTCHEON, M, STRUMIA, M, and MUDD, S Correlation between changes in bacterial surface properties and in phagocytosis caused by normal and immune sera, *Jr Exper Med*, 1929, xlix, 797-810
- ³⁵CHUNG, H L, and REIMANN, H A Antibody formation in kala-azar, *Arch Int Med*, 1930, xlii, 782-786
- ³⁶REIMANN, H A The occurrence of degraded pneumococci in vivo, *Jr Exper Med*, 1927, xlv, 807-814
- ³⁷FITCH, C P, DONHAM, C R, BISHOP, L M, and BOYD, W L Studies of the test tube agglutination test for the diagnosis of Bang's disease, *Technical Bull* 73, *Univ of Minn Agr Exp Sta* 1930, 47
- ³⁸REIMANN, H A Hyperproteinemia as a cause of autohemagglutination, *Jr. Am Med Assoc*, 1932, xcix, (Sept)
- ³⁹MOEN, J K, CHALEK, I, and MEDES, G To be published.

Poisonous Spider Bites

Newer Developments in Our Knowledge of Arachnidism

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INCIDENCE OF ARACHNIDISM

ALTHOUGH poisoning resulting from the bite of a spider has been recognized from the earliest times, and instances were noted in this country more than two hundred years ago,¹⁸⁰ a review of the literature made in 1926 disclosed a remarkable amount of skepticism as to the real existence and seriousness of this condition. At that time more than one hundred and fifty cases of spider bite poisoning reported by more than thirty different observers in the United States were reviewed, fifteen cases studied at the Los Angeles General Hospital were presented, the clinical syndrome was described at length, the course and treatment outlined, and some experimental work on the effect of the venom on small animals was summarized.²²

In the five years that have elapsed since this work was published, arachnidism has become much better known in this country and cases are being recognized and reported with considerable frequency. Thus more than a dozen different authors have published accounts of over seventy-five addi-

tional cases of arachnidism in this country, and numerous reports have appeared in Australia, South America and elsewhere, on this subject. Personal communications have revealed more than a hundred other cases, hitherto unpublished, treated by a score of physicians in California, Florida, and other states.

In view of the fact that nineteen instances of this condition were seen at a single hospital in Los Angeles during the past year, it appears probable that the true incidence of the disease throughout the country annually exceeds hundreds, and possibly thousands, of cases. Several death certificates were made out from this cause in California during the past year and several others reported in the newspapers and in personal communications, so that even though the mortality rate is very low, the possibility of such fatal termination cannot be disregarded.^{11, 17, 120-145}

By far the greatest number of poisonous spider bites in human beings have been attributed to the black widow, or shoebutton spider, the female *Latrodectus mactans*, and to related species in other countries. It is true that a few instances of poisoning due

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TABLE I
Poisonous Spider Bites in the United States

STATE	CASES	DEATHS	STATE	CASES	DEATHS
Alabama	17	0	Nebraska	0	0
Arizona	x	0	Nevada	x	0
Arkansas	6	0	New Hampshire	x	0
California	250	12	New Jersey	0	0
Colorado	1	0	New Mexico	x	0
Connecticut	0	0	New York	x	0
Delaware	0	0	North Carolina	9	1
Florida	35	0	North Dakota	0	0
Georgia	7	0	Ohio	1	1
Idaho	0	0	Oklahoma	2	1
Illinois	0	0	Oregon	0	0
Indiana	0	0	Pennsylvania	2	0
Iowa	0	0	Rhode Island	0	0
Kansas	2	1	South Carolina	x	0
Kentucky	x	0	South Dakota	0	0
Louisiana	12	0	Tennessee	1	0
Maine	0	0	Texas	5	0
Maryland	1	0	Utah	x	0
Massachusetts	1	0	Vermont	0	0
Michigan	0	0	Virginia	27	1
Minnesota	0	0	Washington	0	0
Mississippi	x	0	West Virginia	1	0
Missouri	0	0	Wisconsin	0	0
Montana	0	0	Wyoming	0	0

Total 380 cases with 17 deaths in 18 states

(x=Black Widow Spider identified but no bites reported)

to the bites of other kinds of spiders have been reported,¹⁴³ but in most instances these bites have resulted in local rather than in general symptoms,¹⁶⁰ and many cases have been so complicated by infection and other factors that a correct evaluation is impossible.²⁷ On the other hand, the female *Latrodectus mactans* has been observed in scores of instances, and its recognition established not only by the very vivid descriptions of the black spider and its red markings given by the patients, but on many occasions the actual specimen has been captured and submitted to competent authorities for identification.

Moreover, the astounding symptoms which develop after the bite of this spider are so striking and unique that there seems to be little danger of confusing it with any other form. Further experimental work with the spider and extracts of the poison glands in our laboratory have, for the most part, confirmed previous findings. The bite of the spider produced marked symptoms, sometimes fatal, in mice as well as in rats, in many but not all of the experiments so performed. As previously reported, however, no consistent effect was obtained by the injection of macerated extracts of the whole spider or of its glands alone into mice,

rats, guinea pigs, rabbits, cats or chickens^{22, 26}

The question arises whether there has been an actual increase in the number of cases of spider bite poisoning in this country, or whether the condition is simply being more often recognized. The numerous occasions

TABLE II

YEARS	No CASES REPORTED
1720	1
1800-1825	0
1825-1850	5
1850-1875	7
1875-1900	116
1900-1925	85
1925-1932	166

on which physicians, being told of the syndrome, recall similar cases which they had seen in the past and failed to diagnose correctly, suggest that the latter explanation is by no means unreasonable. On the other hand, numerous observers have noted an actual increase in the number of the spiders, and particularly a change in their habitat, so that now, instead of being confined mainly to little inhabited rural regions, they appear to have invaded the city homes and are frequently found within garages and bedrooms of populated houses.

Accounts are still being received of patients suffering from the bite of the black widow spider who were subjected to the additional trauma of a major surgical operation because of faulty diagnosis and confusion with acute surgical conditions.^{38, 69, 85, 129, 147} It is, therefore, again in order to call attention to the existence and semiology of this very interesting but not really rare condition.

Altogether sixty patients suffering from the bite of a poisonous spider have been treated at the Los Angeles General Hospital. The findings

TABLE III

Cases of Arachnidism at the Los Angeles General Hospital

YEAR	No CASES
1915	1
1916	0
1917	0
1918	0
1919	1
1920	1
1921	0
1922	1
1923	2
1924	2
1925	8
1926	7
1927	2
1928	2
1929	2
1930	12
1931	19
Total	60

of the earlier studies have been quite consistently confirmed, and additional information has been obtained in this larger group. Most of the patients were men, but seven, or twelve per cent, were females. The ages ranged from one to seventy-two years, but the majority were young adults. The

TABLE IV
Age and Sex

YEARS	MALE	FEMALE	TOTAL
0-9	4	1	5
10-19	9	0	9
20-29	18	2	20
30-39	9	0	9
40-49	5	0	5
50-59	4	2	6
60-69	3	2	5
70-	1	0	1
Total	53	7	60

majority were native white Americans but seventeen Mexicans and five Orientals were included. Nearly half of the patients were common laborers, but six housewives, nine children, and more than a score of skilled workers, including a sheriff, a painter and a teacher were affected.

Most of the bites occurred in the more sparsely settled districts, the majority of them being entirely outside of the city limits of Los Angeles, but instances were noted in the more crowded neighborhoods also. The bites took place, for the most part, in

the evening or early morning in summer or autumn. The spider was seen and described in the majority of instances, but a number of cases were diagnosed from the characteristic clinical picture alone, often confirmed thereafter by a successful search of the premises for the spider.

The culprit was variously described as large, medium sized or small, but always as black, and smooth or shiny, and usually as being marked with red on the abdomen, especially on the ventral side, where the hourglass shape of the red mark was often noted. Many of the spiders, alive or dead, were brought in for recognition. They were located in an outdoor privy in half of the cases, but in this series there were ten patients who were bitten while in their own homes, most of them while in bed. Several cases occurred in automobiles or garages, and in several the spider was found in clothes which had been hanging in exposed places, on porches, garages, in yards, etc.

The site of the bite was on the penis or neighboring structures in half of the cases, but the extremities were bitten in sixteen instances, the body ten times and the head twice. This is a much higher incidence of extragenital localizations than has been previously reported, due to the fact that the spiders in the more recent cases has been found more often in situations other than the classical one beneath the seat of an outdoor privy.

The diagnosis was made with little difficulty in these cases, no other condition being even suggested in most of the more recent instances, even in the absence of a history of seeing the

TABLE V
Incidence of Poisonous Spider Bites
By Months

January	0
February	0
March	2
April	3
May	5
June	6
July	9
August	13
September	8
October	8
November	3
December	3
<hr/>	
* Total	60

TABLE VI
Diurnal Incidence of Arachnidism

A M	12- 1	2	P M	12- 1	2
	1- 2	0		1- 2	0
	2- 3	0		2- 3	0
	3- 4	2		3- 4	2
	4- 5	0		4- 5	4
	5- 6	1		5- 6	2
	6- 7	4		6- 7	2
	7- 8	2		7- 8	4
	8- 9	1		8- 9	6
	9-10	4		9-10	5
	10-11	2		10-11	2
	11-12	3		11-12	4
No record	6	Total			60

spider, but in the earlier cases various abdominal conditions, ruptured gastric or duodenal ulcers, appendicitis with peritonitis, or renal or biliary colic were repeatedly suggested, as well as tabetic crises, food poisoning, pleurisy or pneumonia, and tetanus. Local infections with cellulitis or lymphangitis supervened in four instances.

DIFFERENTIAL DIAGNOSIS

The diagnosis of arachnidism due to the bite of the *Latrodectus mactans* spider depends upon

1 A history of exposure to, or actual experience of, the bite of the black spider. There is usually little or no visible lesion at the site of the bite.

2 Pain, starting usually in the region of the bite but not always, and spreading until most of the larger groups of muscles of the body are involved. Except in multiparous women, the pain is usually felt most intensely in the abdominal muscles. The pain increases, reaching its maximum about an hour after the bite, and is then evidently excruciating and agonizing, usually continuous but occasionally cramp-like or intermittent and manifested by writhing, doubling up and screaming or moaning.

3 Rigidity and muscle spasm, most notable in the muscles of the abdominal wall, which become board-like and hard, as in general peritonitis. It should be noted, however, that the rigidity is not confined to the abdomen, but that the intercostal muscles may contract, causing a "tightness" of the chest, and the back muscles may contract, causing a backache or stiffness of the back. The spasm of the calf muscles and other muscles of the ex-

trémities may be remarked, and the legs may be drawn up on the abdomen. True local tenderness, however, is usually entirely absent, or disproportionately slight compared to the intensity of the muscle spasm.

4 Increased blood pressure, usually 20 to 40 mm above the normal for that patient, hyperactive reflexes, especially the knee jerk, and an increase in the pressure of the spinal fluid are usually present.

5 A mild rise of body temperature, with occasionally, but not uniformly, a slow pulse, and a definite leucocytosis, with an increased percentage of polymorphonuclear leucocytes and a shift to the left in the Schilling count is to be expected.

6 Profuse perspiration, restlessness and anxiety, tossing about in agony and similar symptoms are usually seen. Nausea and vomiting, localized edema, twitching or spasms of the muscles of the extremities, and priapism and urinary retention are occasionally noted.

If these considerations are borne in mind, it is not usually difficult to distinguish a case of arachnidism from one of an acute surgical abdominal condition, renal or biliary colic, tabetic crises, food poisoning, pneumonia or pleurisy, tetanus, or any of the other conditions that may be suggested.

Poisonous spider bites could be, to a great extent, avoided if the general population were taught that these small and innocuous looking creatures are really dangerous and should not be tolerated in the vicinity of human beings. In order to avoid the unnecessary extermination of the many useful and desirable species of spiders,

the characteristics of this species should be made known and the peculiarities of its web popularized so that it may be readily recognized whenever encountered. This web consists of straggly, uneven, coarse viscous threads running in all directions in all three dimensions, with none of the geometrical exactitude which gives to the orbweavers or sheetweavers their esthetic charm. The poisonous female *Latrodectus mactans* may stretch its slim glossy black legs over as much as two inches spread. The under surface of the black globular abdomen usually bears a bright red patch shaped somewhat like an hour-glass. Once seen it is readily identified. Methods of extermination of the spider include destruction of its web and egg sacs, as well as the spiders themselves, with a broom, shoe, fly swatter or any other solid object available, or by the use of fly sprays or other special poison sprays, and by the encouragement of the natural enemies of the spider, both insects and birds.

Palliative treatment to alleviate the acute pains of spider bite poisoning is always sought, but usually is only partially effective. Opiates were given to most of our patients, but remark is repeatedly made of their relative inefficiency in this condition. Other sedatives and anodynes, including bromides, barbituric acid derivatives, and other coal tar compounds, were also used. The employment of hydrotherapy, in the form of hot baths, hot compresses and other applications, appeared to give considerable relief in many cases. Spinal puncture was performed only in a half-dozen cases, but the immediate relief following it in

most of these instances was so striking that it must be accorded special consideration as a therapeutic measure in this condition. The intravenous injection of a ten per cent solution of magnesium sulphate was given in one instance, with some apparent relief in symptoms.

Blood was taken from about one-third of these patients from one to ten weeks after the bite, and the serum was given to twenty-four patients soon after admission to the hospital. In three instances the treatment was repeated. The doses varied from two to thirty-five c c of this convalescent serum, given intramuscularly. It was administered from two to twenty-two hours after the bite was sustained, the average time being eight hours. The clinicians repeatedly reported that substantial relief from the symptoms followed soon after its administration.

The results of serum therapy in arachnidism are not readily evaluated, because of the variability of the symptoms and the fact that the milder cases might be expected to be more apt to escape this treatment. Analysis of the data available shows that the average

TABLE VII
Interval Between Bite and Onset of Pain

	CONVALESCENT SERUM		TOTAL
	TREATED	UNTREATED	
"Immediate"	8	9	17
"Soon"	4	4	8
0-15 min	2	3	5
15-30 min	4	2	6
30-60 min	2	1	3
60 min -	1	2	3
No record	3	15	18
Total	24	36	60

TABLE VIII
Interval Between Bite and Most Severe Pain

	CONVALESCENT SERUM		TOTAL
	TREATED	UNTREATED	
0-30 min	3	3	6
30-60 min	2	4	6
1- 2 hours	5	6	11
2- 3 hours	2	2	4
3- 6 hours	3	4	7
6 hours-	1	2	3
No record	8	15	23
Total	24	36	60

time of development of the symptoms was practically the same in those receiving the serum from those not so treated, and that the first signs of subsidence of the symptoms appeared after approximately the same interval of time. In the patients who received the serum treatment within eight hours of the bite, the main relief was obtained several hours earlier than in those not so treated, and complete cessation of symptoms and the recovery

from after-effects was somewhat more rapid in the treated group than in those receiving no such treatment.

Nevertheless, just as many clinicians feel that they can well dispense with the use of the antitoxic serum in the ordinary case of scarlet fever, potent and specific as this treatment is acknowledged to be, so it is thought that the convalescent serum in arachnidism, although theoretically correct and practically of apparent clinical value, is not an essential requisite in handling most cases of spider bite poisoning.

Perhaps it should be stated that despite its severe symptoms, spider bite poisoning is, in the majority of cases, a self-limited condition, and generally clears up spontaneously within a few days. Much suffering and even fatalities are due to injudicious treatment rather than to the venom itself. Thus, stimulants, caffeine, strychnine, adrenalin, and especially the lavish use of alcohol have no ra-

TABLE IX
First Relief from Pain

HOURS UNTIL FIRST SIGN OF RELIEF	CONVALESCENT SERUM		UNTREATED	TOTAL
	TREATED IN FIRST 8 HRS	TREATED AFTER 8 HRS		
1	0	0	2	2
2	0	0	1	1
3	1	0	2	3
4	0	0	2	2
5	2	1	3	6
6	1	1	3	5
7	1	0	0	1
8	1	0	1	2
9	0	0	0	0
10	0	0	2	3
11	1	0	0	1
12	0	2	1	3
No record	5	8	10	23
Total	12	12	30	60

TABLE X
Main Relief from Pain

HOURS UNTIL MAIN RELIEF	CONVALESCENT SERUM TREATED		UNTREATED	TOTAL
	IN FIRST 8 HRS	AFTER 8 HRS		
1- 6	1	0	0	1
6-12	2	0	3	5
12-18	5	4	7	16
18-24	1	2	6	9
24 hrs -	2	6	10	18
No record	1	0	10	11
Total	12	12	36	60

TABLE XI
Complete Recovery from Pain

DAYS UNTIL COMPLETE SUBSIDENCE	CONVALESCENT SERUM TREATED		UNTREATED	TOTAL
	IN FIRST 8 HRS	AFTER 8 HRS		
0-1	1	2	3	6
1-2	2	2	3	7
2-3	4	2	5	11
3-4	1	5	2	8
4-5	0	0	4	4
5-6	0	0	3	3
6-	0	0	4	4
No record	4	1	12	17
Total	12	12	36	60

TABLE XII
Duration of Hospital Stay

DAYS IN HOSPITAL	CONVALESCENT SERUM TREATED		UNTREATED	TOTAL
	FIRST 8 HRS	AFTER 8 HRS		
0- 1	1	0	1	2
1- 2	3	0	7	10
2- 3	3	1	9	13
3- 4	1	4	4	9
4- 5	3	3	3	9
5- 6	1	2	4	7
6- 7	0	1	3	4
7-	0	1	5	6
Total	12	12	36	60

tional indication and are probably productive of more harm than good in this condition. Similarly, local treatment by incision, caustic chemicals, and even the actual cautery, is practically always too late to be of any value since the venom is so rapidly absorbed that systemic effects develop within a few minutes and generally reach their acme within an hour after the bite. On the other hand, such treatment is apt to open the way to local infection, since the spider usually lives in dirt and filth and the site of the wound is apt to be contaminated with germs. Since there is little or no local lesion, the simple application of any mild antiseptic, such as tincture of iodine, is preferable. The fact that four of our cases of spider bite poisoning thereafter developed local infections at the site of the bite, and others have reported deaths from similar infections, emphasizes the desirability of such local antiseptic application.

CONCLUSIONS

The black widow spider is found over more than half of the United States. Nearly four hundred instances of systemic poisoning from its bite have been reported. Unnecessary operations upon such patients could be avoided if all physicians recognized that an acute condition with rigidity of the abdomen, fever and leucocytosis, and occasionally nausea and

vomiting, may supervene as a result of the bite of a black spider. It may be differentiated, however, from acute abdominal lesions requiring surgical intervention by the presence of spasm in muscles other than those of the abdomen, by the absence of marked local abdominal tenderness, and by the concomitant rise in the pressure of the blood and spinal fluid. The mortality rate is low and patients usually recover spontaneously within a few days, but the suffering is intense and more than a dozen fatalities have been reported. Sixty patients have been treated at the Los Angeles General Hospital with no deaths.

The prevention of arachnidism depends upon popular education as to the danger of these spiders and the advisability of their eradication. Local treatment of the bites should consist of simple antiseptic applications, and additional trauma by incisions, cauterization, or the injection of hypothetical antidotes should be avoided. Stimulation and alcoholic drinks are usually contraindicated. Harmful surgery may be obviated by correct diagnosis. Opiates and hypnotic drugs may be used as palliative measures, together with sedative hydrotherapy and the reduction of intracranial pressure by the administration of hypertonic solutions or spinal puncture. Specific treatment with serum from convalescent victims is of value, particularly if administered early.

REFERENCES

- (Reprints of "Arachnidism" by Emil Bogen, 1926, containing 462 additional references, may be obtained from the author.)
¹ALDROVANDI, U. De animalibus insectis libri septum, cum singulorum iconibus

- autore Aldrovando, 1602, J. B. Bellagambini, Bononiæ.
²AMARAL, A. Specific antivenins to combat scorpionism and arachnidism. Bull. Antivenin Inst. Am. 1928 II 69.

- ³ANDRE, E Sur la piqure des chélicères, Zool Anz, 1908, xxxiii, 289
- ⁴ANONYMOUS Symptoms following the bite of a red-backed spider, Lactrodecus species, Health, 1925, iii, 88
- ⁵ANONYMOUS Bibliography of poisonous spiders of Brazil, La Nature, 1926, liv, 239
- ⁶ANONYMOUS Bites from poisonous spiders, Sci, (Science News), 1926, ns 64, supp 10, x
- ⁷ANONYMOUS Denizens of the chaparral, Los Angeles Times, April 5, 1931
- ⁸ANONYMOUS Spider poisoning cases reported, Weekly Bull Cal State Dep't Public Health, 1930, ix, 113
- ⁹ARNETT, C L Black widow spider spray, Advertising circular, 1931
- ¹⁰ARNETT, C L The people versus the widow, San Bernardino Daily Sun, Feb 25, 1932, 5
- ¹¹ARNETT, C L Personal communication reporting fatal cases, 1931
- ¹²BAERG, W J The black widow, Nature Mag, 1929, xiv, 152
- ¹³BALFOUR, A Tropical problems in the new world, Tr Roy Soc Trop Med and Hyg, 1914-15, viii, 75-110
- ¹⁴BALFOUR, A Correspondence the red-backed spider, Med Jr Australia, 1927, i, 873
- ¹⁵BARRINGER, P B Discussion, Va Med Monthly, 1930, lvi, 791
- ¹⁶BAYS, J Spider bite, case, Jr Med Assoc So Africa, 1931, v, 529
- ¹⁷BEASLEY, R N Death from bite of a trapdoor spider, Med Jr Australia, 1930, i, 255
- ¹⁸BERLAND, L Contribution a l'étude de la biologie des Arachnides, Ann Soc ent fr, 1922, xci, 193-208
- ¹⁹BERLAND, L Le venin des araignees, Rev Sci, 1927, lvi, 267 Also in La Nature, 1927, lii, 330
- ²⁰BISHOP, F C Waging war on insect enemies of man and animals, Tr Ent Soc Am 1931
- ²¹BOGEN, E Arachnidism, a study in spider poisoning, Jr Am Med Assoc, 1926, cxviii, 1894
- ²²BOGEN, E Arachnidism Spider poisoning Prize essay of the Cal Med Assoc, 1926, Arch Int Med, 1926, xxxviii, Bibliography in reprints only
- ²³BOGEN, E Correspondence Possible arachnidism Jr Am Med Assoc, 1927, lxxxix, 50
- ²⁴BOGEN, E The dangers of spider bite, (Unpublished) Am. Entomol Soc, Dec 1931
- ²⁵BOGEN, E, and BERMAN, P Poisonous spider bites, Cal and West Med, 1927, xxvi, 339
- ²⁶BOGEN, E, and MANER, G D The action of spider poison, (Unpublished) Cal Med Assoc, 1926
- ²⁷BON On the silk of spiders, Phil Tr Roy Soc London, 1722, v, 21
- ²⁸BROWN, G R Black widow, Nature Mag, 1928, xi, 156.
- ²⁹BROWN, G R Poison "Pokomoo," Los Angeles Times, Sept 20, 1931
- ³⁰BROWNE, A C The black widow, Monthly Bull Cal Dept Agric, 1930, xix, 596
- ³¹BROWNING, W H Arachnidism, spider poisoning, New Orleans Med and Surg Jr, 1930, lxxxii, 873
- ³²BRUMFIELD, W A Discussion, Va Med Monthly, 1930, lvi, 791
- ³³BRAZIL, V, and VELLARD, J Das Gift der brasilianischen Spinnen, Seuchenbekämpfung, 1930, vii, 12, 96, and 158
- ³⁴BRAZIL, V, and VELLARD, J Contribuição ao estudo do veneno das aranhas, Mem Inst de Butantan, 1926, iii, 243-294 Abstract in Ber ges Physiol u exper Pharm, 1926, xli, 432
- ³⁵BRAZIL, V Action coagulante et anticoagulante des sérums coagulabilité des plasmas normaux, Ann de l'Inst Pasteur, 1928, xlii, 907-944
- ³⁶BYERS, W Personal communication reporting cases, 1931
- ³⁷CAIDWELL, C W Death of from septicemia following spider bite, Jr Am Med Assoc, 1924, lxxxi, 1260
- ³⁸CARRINGTON, G L Bilateral diaphragmatic pleurisy simulating perforated gastric ulcer, Jr Am Med Assoc, 1927, lxxxviii, 1395
- ³⁹CATALAN, E Arañas venenosas, Rev Chilena de hist nat, 1916, xx, 58
- ⁴⁰CHILAND, J B Sixth annual report of the gov't bureau of microbiology, in

- report of director public health, New South Wales, 1915-1916, 270
- ⁴¹CLELAND, J B Inquiries and diseases in Australia attributable to animals other than insects, *Med Jr Australia*, 1932, 1, 157
 - ⁴²COUSTAN Quelques notes sur l'araignée rouge de Curacao, *Arch Med Nav*, 1868
 - ⁴³CREMER, C L Beitrag zu den Vergiftungen durch Schlangen und Spinnenbisse, *Schmidts Jahrb*, 1870, cxlvi, 238, and 1880, ccxxv, 239
 - ⁴⁴CRESPIGNY, C T Ch de Discussion, *Med Jr Australia*, 1929, 11, 486
 - ⁴⁵CULPEPPER So Med, 1925, Abstracts in *Ann d'Hyg*, 1925
 - ⁴⁶DARNELL, J C Black widow spider, *Flower Grower*, 1929, xvi, 254
 - ⁴⁷DE GEER, C Memoires pour servir à l'histoire des insectes, 1752-1778, L L Grefing, Stockholm
 - ⁴⁸DRENSKI, L Le venin des araignées et leur action sur l'organisme animal, *Tr Soc Bulg sci nat*, 1915, vii, 152
 - ⁴⁹ELLIS, J B Arachnidism, five cases of spider poisoning, *ANN INT MED*, 1930, 111, 924
 - ⁵⁰FABRE, J H Nouveaux souvenirs entomologiques, 1882, C Delgrave, Paris
 - ⁵¹FAIRFAX, N The innoxiousness of spiders and toads, *Phil Tr Roy Soc*, London, 1700, 11, 800
 - ⁵²FAUST, E S Die tierische Gifte, 1906, F Vieweg und Sohn, Braunschweig
 - ⁵³FAUST, E S Darstellung und Nachweis tierischer Gifte, *Handb der Biochemes Arbeitsmethoden*, 1909, 11, 837
 - ⁵⁴FAUST, E S Tierische Gifte, *Handb der exper Pharmak*, 1924, 11, 1748
 - ⁵⁵CALMETTE, A, und BRUYANT, L Vergiftungen durch tierische Gifte, *Handb der Tropenkrankheiten*, 1927, 11
 - ⁵⁶FAUST, E S Vergiftungen durch tierische Gifte, *Handb der Inn Med*, (Ed Bergmann, R V, and Stacheln, R), 1927, 11, J Springer, Berlin
 - ⁵⁷FOLQUER, H Caso mortal de aracnoidismo en el lactante, *Bol Inst de clin quir*, 1928, 11, 699-704
 - ⁵⁸FONTANA Quoted by Mitchell, reporting fatal cases, 1781
 - ⁵⁹FORELL, *Bull Soc vaudoise sci nat*, 11
 - ⁶⁰FULLAWAY, D T Poisonous spider in Hawaii, *Hawaiian Forest*, 1926, xxiii, 66
 - ⁶¹FULLBORN, VON (Review of Baerg's work), *Arch f Schiffs- u Tropen-Hyg*, 1924, xxviii, 128
 - ⁶²FYFFE The bite of the Kaptipo, *Tr New Zealand Inst*, 1901 xxxiii, 436
 - ⁶³GUINARAES, J L *Gazeta Clin*, São Paulo, 1903
 - ⁶⁴HECKER, J F C Die Tanzwuth, 1832, T C F Enslin, Berlin
 - ⁶⁵HECKER, J F C Memoire sur la choree épidémique du Moyen Age, *Ann d'Hyg*, 1834, 11, 312-390 also in "Die grossen Volkskrankheiten des Mittelalters," 1865, T C F Enslin, Berlin, 163
 - ⁶⁶HALES, G M B Correspondence Red-backed spider bite, *Med Jr Australia*, 1928, 1, 194
 - ⁶⁷HALES, G M B Discussion, *Med Jr Australia*, 1929, 11, 486
 - ⁶⁸HALL, W Personal communication reporting cases
 - ⁶⁹HALL, E M Personal communication reporting operated case
 - ⁷⁰HERRICK, G W Insects injurious to the household and annoying to man, 1926, The Macmillan Company New York, 404
 - ⁷¹HOLMES, and COURT, A W Discussion, *Med Jr Australia*, 1929, 11, 486
 - ⁷²HOUSSAY, B A Contribution a l'étude de l'hémolysine des araignées, *Compt Rend Soc de biol*, 1916, lxxix, 658
 - ⁷³HOUSSAY, B A Arañas venenosas, *Actas Cong Soc Hig Micro y Patol*, 1916 *Rev de Med*, Rosario 1917
 - ⁷⁴HOUSSAY, B A Datos complementarios sobre la acción fisiológica del veneno de la araña Theraphosa, *Prensa Med-argent*, 1917, 11, 18-19
 - ⁷⁵HOUSSAY, B A Nuevos datos sobre las hemolisinias de las arañas, *Prensa Med-argent*, 1917, 11, 370-371
 - ⁷⁶HOUSSAY, B A Activación por los huevos de araña de la acción hemolítica de los venenos de víbora, *Prensa Med-argent*, 1917, 11, 382-383
 - ⁷⁷HOUSSAY, B A Observaciones a algunas opiniones corrientes sobre los peligros de las arañas venenosas *Semin Med* Buenos Aires, 1917 xxii : 3-2
 - ⁷⁸HOUSSAY, B A Sur les propriétés de ven-

- lytiques, fermentatives et toxiques des extraits d' araignées, Bull Soc path exot, 1918, xi, 217-239
- ⁷⁹HOUSSAY, B A, and NEGRETE, J Estudios experimentales sobre la accion fisiological de las ponzanas de las arañas, Rev d inst bact, 1919
- ⁸⁰HOUSSAY, B A, and NEGRETE, J Estudios experimentales sobre la accion de los venenos de las arañas, Treb Soc Biol, Barcelona, 1922, vi, 194
- ⁸¹HUTCHESON, L Effect of spider bite on man, Entomolog News, 1916, xxvii, 464
- ⁸²IHERING, R VON Aranhas et outros arachnoides do Brazil que determinam evenamento, Ann paulist de med e cir, 1916, vii, 5-9
- ⁸³JACKSON, E S The red-backed spider bite, Med Jr Australia, 1927, i, 525
- ⁸⁴JONES, M A The black widow moves in, Better Homes and Gardens, 1931, ix, 37
- ⁸⁵JONES, J B Discussion, Va Med Monthly, 1930, lvi, 791
- ⁸⁶KELLAWAY, C H The bite of Latrodectus hasseltii, Med Jr Australia, 1929, ii, 486
- ⁸⁷KELLAWAY, C H The venom of Latrodectus hasseltii, Med Jr Australia, 1930, i, 41
- ⁸⁸KLINGER Cited by Walbum
- ⁸⁹KOBER, R Über die giftigen Spinnen Russlands, Biol Zentralbl, 1888, viii, 287-288
- ⁹⁰KOEPPEN Über einige in Russland vorkommende giftige und vermeintlich giftige Spinnen, Beitr z Kenntnis des Russ Reiches, 1881, iv, 180
- ⁹¹KRAUS, R 10 Jahre Sudamerika, 1927, G Fischer, Jena
- ⁹²LARA, A Algunos Puntos de Patologia Tropical, Rev med de Yucatan, Merida, 1926
- ⁹³LEGNANI, M Carbunclo de araña, Rev med d Uruguay, 1917, xx, 375-383
- ⁹⁴LEITAO, M Theraphosideas do Brasil, Rev Mus Paulista, São Paulo, 1923, xiii, 1-438
- ⁹⁵LETHBRIDGE, H V Correspondence, the red-backed spider, Med Jr Australia, 1927, i, 654
- ⁹⁶LETHBRIDGE, H V Discussion, Med Jr Australia, 1929, ii, 486
- ⁹⁷LÉVY, R Sur le mecanisme de l'hemolyse par l'arachnolysine, Compt rend. Acad d sci Par, 1912, cliv, 77
- ⁹⁸LÉVY, R Relations entre l'arachnolysine et les organes genitaux femelles des araignées, Compt rend Acad d sci Par, 1912, clv, 233
- ⁹⁹LÉVY, R Sur les toxines des araignées et particulièrement des Tégénaires, Compt rend Acad. d sci, Par, 1916, clxii, 83-86
- ¹⁰⁰LÉVY, R Contribution à l'étude des toxines chez les araignées, Paris Ann. sci nat Zool, 1916, Ser 10, 161-399 et Thèse Faculté sciences Paris
- ¹⁰¹LEEUWENHOEK, A VAN Experiments with spiders and frogs, Phil Tr Roy Soc London, 1702, xxii, 867
- ¹⁰²LUDEKING Over Mygale sumatrense en hare beet, Natuurk Tijdschr. Ned Ind, 1859, xx, 191-192
- ¹⁰³MCKAY, S Correspondence, the red-backed spider bite, Med Jr. Australia, 1927, i, 626
- ¹⁰⁴MARTINO Esperience sul istinto e sullo morso della Tarentula de Puglia, Il Filiatre-sebezio, 1849.
- ¹⁰⁵MATUS, M Mancha gangrenosa, Bol Soc de Cir de Chile, 1927, v, 75-78
- ¹⁰⁶MAZZA, S Necrosis considerable producida por picadura de araña migalomarfa, Bol Inst de clin quir, 1927, iii, 767-769
- ¹⁰⁷MAZZA, S Arachnoïdisme, Cong internat de path comp, 1914, ii, 276-278
- ¹⁰⁸MAZZA, S Contribucion al estudio del aracnoïdismo, Rev de la San Mil, Buenos Aires, 1910
- ¹⁰⁹MIGUEL, Sobre la araña venenosos de Chile, Ann de la Univ de Chile, ix
- ¹¹⁰MILES, S Personal communication reporting cases, 1930
- ¹¹¹MILES, E H Correspondence, the red-backed spider bite, Med Jr Australia, 1927, i, 353
- ¹¹²MITCHELL, C A The venom of spiders, Knowledge and Ill Sci News, 1905, ii, 298, and 1906, iii, 316
- ¹¹³MOORE, O M Personal communication reporting cases, 1926
- ¹¹⁴MOORE, S P Treating poisonous bites with antitoxin, Nations Health, 1927, ix, 45

- 115MORTON, C B Personal communication reporting cases, 1930
- 116MUSGRAVE, A Some poisonous Australian spiders, *Rec Australian Mus*, 1927, xvi, 33
- 117MUSGRAVE, A Harmful Australian spiders, *Australian Mus Mag*, 1927, iii, 134
- 118PALMER, H E Spider poisoning from bite of *Latrodectus mactans*, *Jr Fla Med Assoc*, 1930, xvii, 64 Also in *Internat Jr Med and Surg*, 1929, xlii, 570
- 119PAVLOVSKIJ, E Ein Beitrag zur Kenntnis der Giftdrüsen der Arthropoden, *St Petersburg Trav Soc nat Sect zool*, 1913, xliii, 175-179
- 120PAVLOVSKIJ, E Gifttiere und ihre Giftigkeit, 1927, G Fischer, Jena
- 121PAVLOVSKIJ, E Experimentelle Untersuchung über die Wirkung des Bisses der Walzenspinne *Galeodes araneoides* auf den Menschen, *Ztschr f Parasitenk*, 1930 iii, 8-16
- 122PENNA, J Comm Cong Int Med d'Hyg, Buenos Aires, 1910
- 123PEPLE, W L Arachnidism, case simulating diffuse peritonitis, *Va Med Monthly*, 1930, lvi, 789
- 124PHISALIX, MME MARIE Effets physiologiques du venin de la Mygale de Corse - et d'une grand Mygale du Hariti, *Bul Mus*, Paris, 1912, 134-138
- 125PHISALIX, MME MARIE Animaux venimeux et venins, 1922, Masson & Cie, Paris
- 126POLLOCK, F On the habits of some Madeira spiders, *Ann and Mag Nat Hist*, 1872, x, Ser 4, 271-274
- 127PRADO, A Quoted by Guzman, reporting cases
- 128PREY, D Arachnidism, *Col Med*, 1930, xxvii, 400
- 129PULFORD, S Personal communication reporting cases, including one fatal case with autopsy findings, 1931
- 130RABAUD, E L'instinct paralysateur des araignees, *Compt rend Acad d sci*, 1921, clxxii, 281
- 131RACOWITZA Quoted by Berland, reporting cases
- 132RAU, P Some life history notes on the black widow spider, *Latrodectus mactans*, *Psyche*, 1924, xxxi, 162-166
- 133RICARDO, T Quoted by Brazil reporting cases, 1901
- 134RILEY, C V, and JOHANNSEN, O A Handbook of medical entomology, 1915, Comstock Publishing Co, Ithaca, New York
- 135ROBERTS, H A Spider venom, *Homeopathic Rec*, 1931, xlii, 637
- 136ROBIE, T An instance of the venom of spiders, *Phil Tr Roy Soc London*, 1726, vi, 52
On the effects of inoculation, the eclipse of the sun in November 1722, and the venom of spiders, *Phil Tr Roy Soc London*, 1724, vii, 20-21
- 137RODRIGUEZ, R Clinical study of cases of spider bite, *Bol Inst de clin quir*, 1928, iv, 697
- 138RODWAY, F A Correspondence The red-backed spider, *Med Jr Australia*, 1922, i, 54
- 139RODWAY, F A Correspondence The red-backed spider, *Med Jr Australia*, 1927, i, 770
- 140SAVAGE, E Personal communication reporting cases, 1931
- 141SAVORY, T H Will you step into my parlor, *Discovery*, vi, 231
- 142SAVORY, T H The biology of spiders, 1928, The Macmillan Co, New York
- 143SCHMAUS, L F Arachnidism, case, *Jr Am Med Assoc*, 1929, xcii, 1265
- 144SHAW, M C Garden spiders, *Flower Grower*, 1929, xvi, 33
- 145SIMON, E Sur l'araignée venimeuse de Bolivie, *Compt rend Soc ent de Belgique*, 1886
- 146SMART, E P Personal communication reporting cases, 1929
- 147SMITH, C E Personal communication reporting operated cases, 1930
- 148STORER, T I Personal communication reporting fatal cases, 1931
- 149SWEANY, H Personal communication reporting cases, 1931
- 150SUTHERLAND, J W Treatment of red-back spider bite, *Med Jr Australia*, 1921, ii 632 and 1922, i, 84
- 151THORILL, T Remarks on venom of European spiders 1870-1873, C I Lundstrom, Upsala 500

- ¹⁵²TIDSWELL, F Researches on Australian venoms, Sydney, 1906
- ¹⁵³TIDSWELL, F. Australian venoms, The Guardian, Feb 18, 1927
- ¹⁵⁴TORRES, O Algumas observacoes sobre a biologia das aranhas do Genera Theraphosa, Rev. de la Soc Bras de sci, Rio de Janeiro, 1921
- ¹⁵⁵TORRES, O Contribucao ao estuda de algunas lesoes determinadas pelos arthropodos, An da 2º Conf Sud Am de Derm e Syph, Montevideo, 1921
- ¹⁵⁶TROISE, E Pharmacodynamic action of venom of spider, Latrodectus mactans, Rev Soc argent de biol, 1928, iv, 447, also in Compt rend Soc del Biol, 1928, xcix, 1431
- ¹⁵⁷TROISE, E Active serum against venom of spider, Latrodectus mactans, Rev Soc argent de biol, 1928, iv, 467 Also in Compt rend Soc de biol, 1928, xcix, 1433 Reviewed in Jr Am Med Assoc, 1929, xcii, 1097.
- ¹⁵⁸TROISE, E Pharmacodynamic action of venom of spider, Latrodectus mactans, Rev Soc argent de biol, 1929, v, 616, also in Compt rend Soc de biol, 1930, cii, 1097
- ¹⁵⁹TROISE, E Specificity of active serum against venom of spider, Latrodectus mactans, Rev Soc argent de biol, 1929, v, 605, also in Compt rend Soc de biol, 1930, cii, 698
- ¹⁶⁰TURPIN, T J Correspondence black spider poisoning, Jr Am Med Assoc, 1921, lxxvi, 954
- ¹⁶¹VANCE The red-backed spider, Med Jr Australia, 1922, i, 113
- ¹⁶²VAUGHN, J T Arachnidism, two cases, Va Med. Monthly, 1931, lvi, 806
- ¹⁶³VELLARD, J Études de Zoologie, Arquivo do Instituto Vital Brasil, 1924, ii, Nos 1, 2
- ¹⁶⁴VELLARD, J, et BRAZIL, V Contribution à l'étude du venin des araignées, Mem Inst de Butantan, São Paulo, 1926, iii, 295-299
- ¹⁶⁵VELLARD, J Bol Inst Vital Brazil, Niteroi, 1929
- ¹⁶⁶WALBUM, L E Der Einfluss der Eiweisskonzentration auf die Resorptionsgeschwindigkeit der Antikörper bei subkutaner und intramuskularer Injection, Ztschr, f Immunitätsforsch. u exper Therap, 1912, xii, 546-564
Untersuchungen über die Gifte der Kreuzspinne (Epeira diadema Walck), ibid 1915, xxiii, 623-684
- ¹⁶⁷WALBUM, L E Weitere experimentelle Untersuchungen über die Gifte der Kreuzspinne (Epeira diadema Walck), Ztschr f Immunitätsforsch u exper Therap, 1915, xxiii, 623-684
- ¹⁶⁸WALSH, G Arachnidism Case of poisoning from bite of Latrodectus mactans, So Med Jr, 1930, xxiii, 1038 Bull Jeff Co Med Soc, 1930, and also personal communication reporting additional cases, 1931
- ¹⁶⁹WATKINS, A Correspondence, Med Jr Australia, 1927, i, 873
- ¹⁷⁰WILKINSON, W W Discussion, Va Med Monthly, 1930, lvi, 791

Studies on a Urinary Proteose

II. Skin Reactions and Therapeutic Applications in Hay Fever

By

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THE literature prior to 1919 dealing with the antigenic properties of protein cleavage products has been thoroughly reviewed by Fink¹ He briefly summarizes the numerous papers reviewed by stating that experiments with products of protein digestion show that proteins cannot be disintegrated much, if any, beyond the coagulable form without losing their sensitizing properties By experiments in which he prepared proteoses from egg albumin he demonstrated that proteoses have definite antigenic properties Auld,² in 1917, began to advocate the use of non-specific peptone therapy in the treatment of bronchial asthma and since that time he has published numerous papers on various phases of its use He uses the word "peptone" advisedly in that it represents a mixture of proteoses and peptones and he recommends Armour's peptone solution because of its high proteose content³ Many other investigators have used peptone solutions in one way or another for nonspecific desensitization in

the various allergic conditions^{4, 5, 6, 7, 8} Vallery-Radot and Giroud⁹ have used Witte's peptone solution intradermally in the treatment of hay fever

The presence of proteose in the urine excreted during suppurative and febrile conditions, malignancy, and tuberculosis has long been recognized¹⁰ The significance of this observation was not definitely understood although Wells mentions the possibility that the symptoms in these conditions may be due in part to proteose intoxication In 1928 Barber and Oriell¹¹ began to publish observations regarding the appearance of a proteose in the urine excreted during allergic conditions as well as in those just noted These investigators found the presence of the proteose to be the cause of a so-called "ether reaction" which was obtained as a result of extracting urine excreted during allergic symptoms with ether after previously acidulating with sulphuric acid A positive reaction consisted in the appearance of a waxy scum in the ethereal layer beneath the superficial froth In strongly positive tests the tube of urine could be inverted without spilling The more acute the allergic symptoms, the more positive the test They were able to ob-

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tain a precipitate from the ethereal layer by adding an excess of alcohol. Aqueous solutions of this precipitate gave the characteristic chemical tests for proteoses. The clinical significance of this urinary substance has been further investigated by Oriel^{12, 13, 14} and by Oriel and Barber¹⁵. After careful observation and well controlled experimentation they have demonstrated the following in the allergic patient. If the proteose is prepared from urine collected during a period when symptoms are present, his skin will usually respond with characteristic wheal formation after intradermal injection, reinjection will reproduce his allergic symptoms, and desensitization will usually result in an improvement or disappearance of his symptoms, if the proteose is prepared from urine collected when symptoms are not present, none of these phenomena will take place.

We have studied this proteose sensitivity in a variety of conditions^{16, 17} but this paper will deal exclusively with a series of hay fever patients treated during the spring and summer of 1931.

Proteose prepared according to the methods of Oriel and Barber¹⁵ was used as follows for skin testing. Tests were performed upon the volar surface of the forearm beginning with the control (1 cc N/10 sodium hydroxide in 9 cc of Coca's solution) just distal to the crease of the elbow. Below this the proteose dilutions were injected intradermally in the order of their strength at distances of 3 cm from each other. About 0.05 cc of solution was used for each injection. A positive skin reaction is character-

ized by the development of a wheal within from 5 to 10 minutes, from the edges of which one or more pseudopods develop (see figures 1 and 2). At the height of its development, which usually takes place in from 15 to 30 minutes, the wheal is circumscribed by a scarlet flare. The patient sometimes complains of itching. The wheal gradually subsides leaving an erythematous blotch which may not disappear for several hours. In a few instances, especially in the hay fever patients, this area of erythema has gradually increased in size up to 12 hours and has been accompanied by tenderness and a sense of heat. In very sensitive patients, especially those subject to asthma, we have found that a focal reaction may follow either the intradermal test or the subcutaneous injection of too large a dose. Consequently it should be stated that for the past few months we have been resorting to the scratch method of testing for sensitivity in order to avoid untoward reactions. For this purpose we apply a few drops of the N/10 sodium hydroxide-proteose solution to a scratch upon the volar surface of the forearm using N/10 sodium hydroxide as a control.

The initial dosage for desensitization is best arrived at by selecting the dilution next below that which gives the least positive intradermal reaction. The first dose is usually 0.05 cc subcutaneously. Injections are given at from three to four day intervals and the dose is gradually increased or decreased as indicated by the patient's clinical progress. In our experience no focal reactions have developed if desensitization were started with the

weak dilution as indicated. If a focal reaction does occur, the next weaker dilution should be used.

The group of hay fever cases herein presented represents one of the numerous allergic conditions in which we have studied the proteose reactivity. In all we have investigated the proteose sensitivity in over 100 patients including, aside from hay fever, such conditions as asthma, serum sickness, eczema, erythema multiforme, migraine and rheumatoid arthritis. Of these we have found hay fever and eczema the most prompt to yield to proteose desensitization. We feel that the presentation of this series of hay fever cases should be of interest because of the very suggestive results obtained and also because of its possible bearing on the study and therapeutics of allergic diseases.

Case I Male, age 17. Onset of hay fever in early summer. Sensitive to orchard grass, timothy, June grass, lambs' quarter, Kochia, pigweed, pasture sage, and false ragweed. This patient was studied merely as a matter of interest to see if proteose prepared from a case of hay fever would induce a positive intradermal reaction. The test proved to be a plus 2.* Treatment with the proteose was not attempted.

Case II Male, age 21. Onset in early summer. Sensitive to various grasses and giant ragweed. Given pollen injections for hay fever during the previous season with no results. Intradermal proteose test, plus 2. Given proteose injections at biweekly intervals with immediate and complete relief of symptoms. After three weeks the patient moved to Michigan, proteose injections were stopped, and the hay fever returned.

Case III Female, age 29. Onset in early summer. Sensitive to June grass, timothy,

*plus 2=moderate reaction, plus 3=marked reaction, plus 4=very marked reaction

orchard grass, lambs' quarter and Kochia. Intradermal proteose test, plus 2. Previous pollen desensitization with only fair results. After two injections the symptoms entirely cleared and the patient did not return for further treatment.

Case IV Female, age 30. Onset in early summer. Sensitive to pasture sage, orchard grass, Russian thistle, broad and narrow leaf cottonwood, pigweed and Indian hair tonic. Treated during previous seasons with pollen injections with slight relief and was taking pollen at the time proteose was prepared. Intradermal proteose reaction, plus 3. Proteose administration was started in conjunction with the pollen desensitization with the result that added relief was obtained although hay fever still persisted to a mild degree.

Case V Female, age 29. Onset in early summer. Sensitive to pigweed, Kochia, Russian thistle and lambs' quarter. Pollen injections during the past season with good results. Had frequent attacks of urticaria which became aggravated during hay fever season. A proteose was prepared in March for the urticaria to which she was skin sensitive and from the administration of which she derived some benefit. With the onset of hay fever another proteose was prepared to which she gave a marked intradermal reaction. After the administration of the proteose the hay fever would improve but as the dosage was increased the urticaria would become more pronounced. Consequently the treatment of this particular case was not entirely satisfactory.

Case VI Female, age 8. Onset in early summer. Complicated by asthma during the previous season. Skin tests for pollen sensitivity not done. The intradermal proteose test was violent in that erythema persisted for over 12 hours. Following proteose administration the symptoms cleared completely and there was no recurrence of her asthma.

Case VII Female, age 39. Onset in early summer. Complicated by asthma during previous season. Sensitive to pasture sage, pasture sage, pigweed, Russian thistle and Indian hair tonic. Received pollen injections the year before with only slight relief of hay fever, asthma recurred as

usual Intradermal proteose reaction was plus 4, and was followed after two hours by an aggravation of the symptoms. Proteose desensitization resulted in considerable relief and the asthma was practically absent as compared with the previous year. In August the hay fever became somewhat worse. Although it was possible that certain of the weeds were responsible for this aggravation another proteose was not prepared.

Case VIII Female, age 39. Onset in early summer. Possible pollens concerned in the etiology not determined. Intradermal reaction to proteose was plus 3, and following the test there was an increase in the nasal discharge. Desensitization with the proteose resulted in a great improvement, the patient suffering only an occasional attack.

Case IX Female, age 17. Onset in early summer. Complicated by chronic sinusitis. Sensitive to many of the grasses and to Russian thistle. Desensitization with pollens gave no relief in 1928, 1929 or 1930. Intradermal reaction to proteose, plus 3. Relief from desensitization was complete for one month and a half (the middle of August) when mild symptoms returned. A second proteose solution was not prepared.

Case X Male, age 45. Onset in early summer. Sensitization tests for the pollens not done. Intradermal reaction to proteose, plus 3. Relief from desensitization was considerable though not complete.

Case XI Female, age 35. Onset in early summer. Complicated by acne. Pollen sensitization tests had been performed before but results were not known to the patient. Previous desensitization gave no relief. Intradermal proteose reaction was plus 4, the erythema increasing up to 12 hours. Relief after desensitization was complete and it was also of interest to note that the acne cleared completely and there was improvement in the general condition.

Case XII Female, age 33. Onset in late summer. Pollen desensitization every year since 1925 gave good results. Intradermal proteose reaction, plus 3. Complete relief obtained after proteose desensitization.

Case XIII Male, age 52. Onset of symptom in late summer. No information

as to pollen tests or previous treatment. Intradermal proteose reaction was plus 4. Marked relief obtained following proteose desensitization.

The most important features concerning this series of cases are summarized in the accompanying table.

It has been recognized that only certain organs of the body may exhibit allergic manifestations. Bronchial musculature or nasal mucous membrane may be sensitive to a given antigen while the skin may or may not show an allergic response.

Alexander¹⁸ reviews this matter quite completely and points out that while the skin test is not always of much help in such conditions as asthma, urticaria and eczema, it is quite reliable in hay fever (between 90 and 95 per cent of the cases). None of our hay fever cases gave a negative or questionable dermal reaction. The standards for the interpretation of the intradermal test must, of course, be arbitrary. We interpret the responses as slight, moderate, marked and very marked, or plus, plus 2, plus 3, and plus 4, respectively. Reference to figures 1 and 2 will afford an idea as to our standards for judging the degree of reaction. Figure 1 exemplifies a marked (plus 3) and figure 2 a very marked reaction (plus 4). Focal reactions consisting in an aggravation of symptoms occurred in cases V, VII, VIII, and XII subsequent to the intradermal test. While no asthmatic attacks were induced the possibility of their occurrence must not be overlooked, and since constitutional reactions may assume serious proportions it should be stated again that we have decided to abandon the intra-

SUMMARY OF RESULTS
OBTAINED BY PROTEOSE DESSENSITIZATION IN HAY FEVER

CASE NO	INTRADERMAL REACTION	FOCAL REACTION	ONSET OF HAY FEVER	TIME UNDER OUR OBSERVATION	INTERVAL FOR THERAPEUTIC RESPONSES	DEGREE OF RELIEF OBTAINED	MISCELLANEOUS
I	2 plus	0	Early				
II	2 plus	0	Early	3 weeks	24 hours	Complete	To Michigan where symptoms returned
III	2 plus	0	Early	3 months	24 hours	Complete	Received only 2 proteose injections
IV	3 plus	0	Early	2 months	2 weeks	Partial	Pollens given simultaneously Proteose gave added relief
V	3 plus	+	Early	4 months	1 week	Partial	Complicated by urticaria One improved at expense of other
VI	4 plus	0	Early	4 months	1 week	Complete	Asthma previous summer No asthma after proteose desensitization
VII	4 plus	+	Early	2 months	1 week	Partial	Very little asthma as compared to the year before
VIII	3 plus	+	Early	1 month	1 week	Partial	
IX	3 plus	0	Early	3 months	1 week	Complete until August	Symptoms returned in mid-August
X	3 plus	0	Early	2 months	1 week	Almost Complete	
XI	1 plus	0	Early	3 months	24 hours	Complete	Acne cleared Improvement in general condition
XII	3 plus	+	Late	6 weeks	1 week	Complete	
XIII	4 plus	0	Late	6 weeks	1 week	Almost Complete	

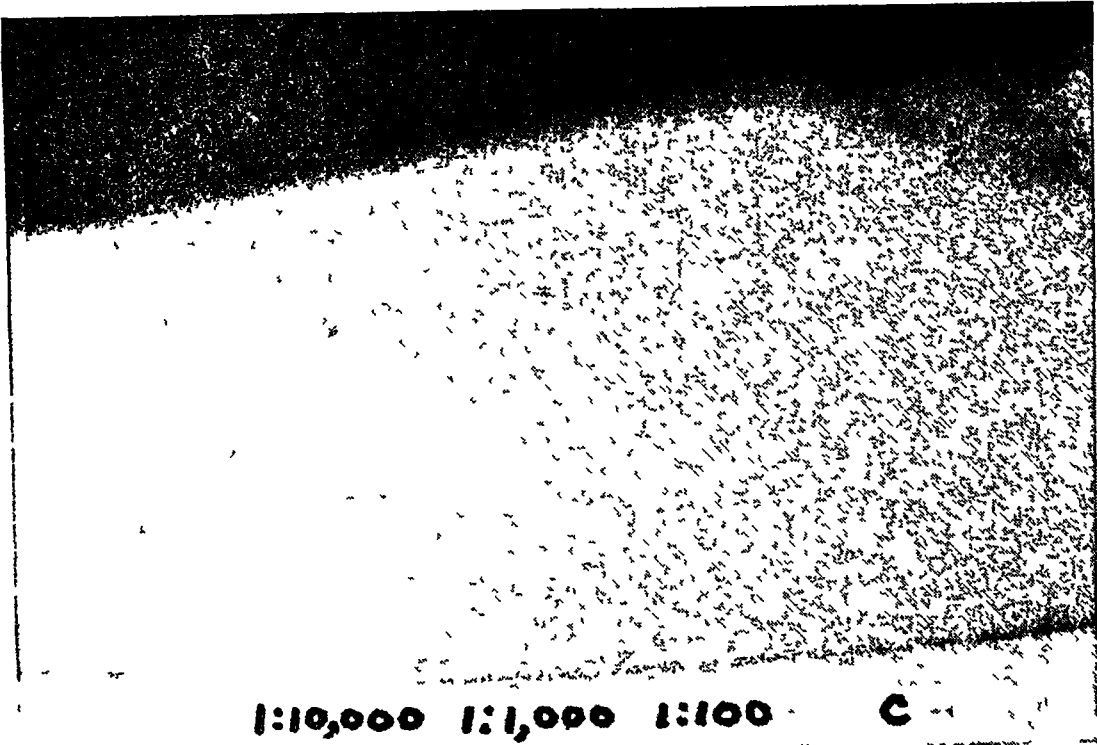


FIG 1 Case VI Intradermal reaction at 15 minutes Interpreted as plus 4

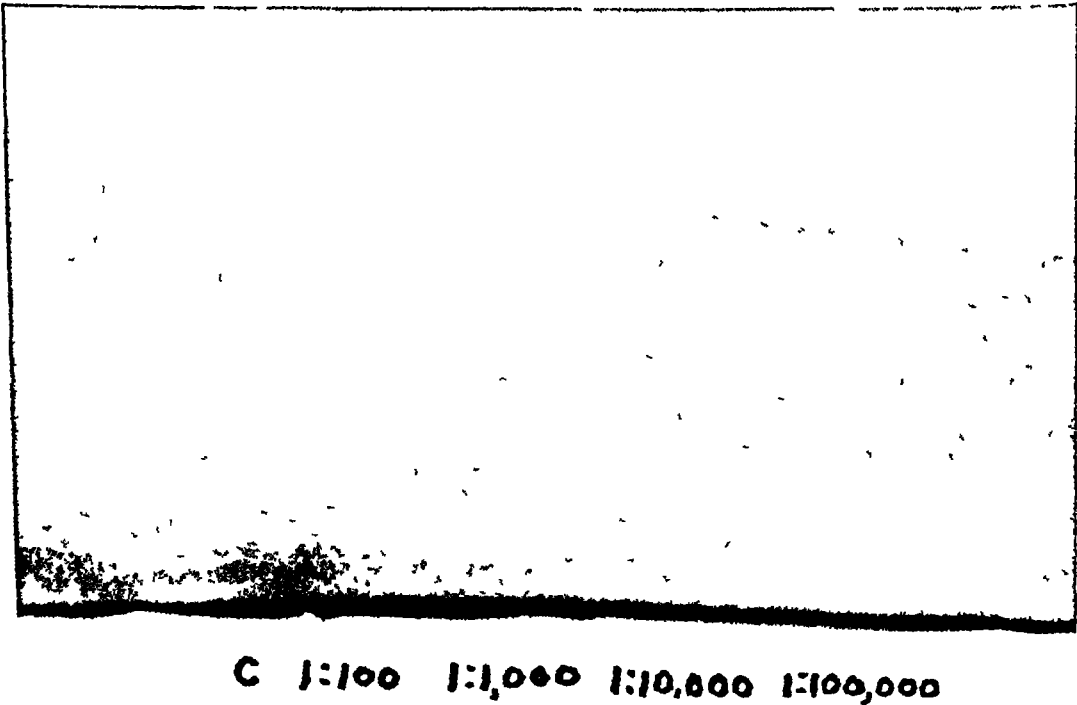


FIG 2 Case VIII Intradermal reaction at 15 minutes Interpreted as plus 3

dermal test in favor of the scratch method

Eleven of the thirteen cases were of the early type of hay fever, two of the late. Where pollen desensitization is attempted the best results are obtained with the early type. Our results do not prohibit the assumption that proteose desensitization would be any less effective in the late than in the early types. The results obtained from pollen desensitization vary somewhat and depend to a certain degree upon the experience and skill of the physician administering the treatment. Thommen,¹⁹ after reviewing the reports of various investigators, gives average results obtained as follows: complete relief 10 to 30 per cent, almost complete relief 24 to 40 per cent, partial relief 20 to 30 per cent, and no relief 9 to 12 per cent. The results obtained from proteose desensitization compare very favorably with those ordinarily obtained following pollen administration. In comparing the results obtained from the two types of therapy it must be remembered that in order to obtain the most satisfactory response to pollen desensitization the patient must be under treatment for from two to three months before the onset of the hay fever is expected. Pollen treatment instituted after the onset of symptoms is frequently unsatisfactory. On the other hand proteose therapy is of value only after symptoms appear. In view of this consideration we feel that the use of the patient's proteose should be a distinct and valuable aid in the management of hay fever.

Furthermore, it is very likely that the use of proteose in the late type of

hay fever would make it possible for a greater number of patients to obtain relief. Case IV suggests another possible use for proteose. This patient received the preseasonal pollen injections for several weeks. When the trees and grasses began to pollinate her symptoms of hay fever appeared. At that time proteose therapy was instituted as a complementary measure. Under this regime, although the symptoms did not entirely clear, she felt that she had obtained definite additional relief. The reason for this added relief may be that the patient was sensitive to pollens which were not included in treatment initiated earlier in the spring. Cases VII and IX obtained great relief early in the summer, but with the pollination of the weeds later in the season the hay fever returned. The observations made in these cases strongly suggest a specific relationship between the various pollens and their corresponding proteoses. Cases V and XI presented certain other very interesting points relative to the specificity of the urinary proteose. Case V was complicated by urticaria which had been present for some time prior to the onset of hay fever. It is probable that proteose prepared after the onset of hay fever had antigenic substances present which were also associated with the urticaria. Since a dosage that seemed to cause improvement in the hay fever appeared to aggravate the urticaria, it is assumed that the respective antigenic substances were specifically related to the two conditions and that they were present in conflicting concentrations which precluded the attainment of satisfactory

results. On the other hand Case XI demonstrated quite the opposite in so far as results were concerned. The patient had had acne for years. Desensitization resulted in complete relief of both and to date (March, 1932) the acne has not returned. It is also of interest to note that her general condition has greatly improved. Here again it is to be assumed that antigens were obtained in the proteose which were concerned in the production of acne as well as hay fever.

Conclusions such as these strongly support the contention that desensitization with the allergic patient's own proteose is based upon the principles of specific therapy.

The use of nonspecific protein desensitization in an effort to counteract reactivity to specific proteins has undoubtedly played a most important rôle in the treatment of allergic disease. Auld²⁰ has recently advocated the use of a special "serum peptone" which is partially prepared from the patient's own blood. If a normal individual eats eggs 48 hours after being injected intracutaneously with serum from an egg sensitive patient, a wheal will develop at the site of the injection. This is a variation of the Prausnitz-Kustner reaction and demonstrates the fact that specific antigenic substances are circulating in the blood stream. If this is true they must be present to a certain extent in the peptone which Auld describes. From the same standpoint the use of auto-hemo-therapy as advocated by Kahn and Emsheimer,²¹ Henske²² and Ghosal²³ is also in part specific in its principle. Flandin²⁴ strongly advocates intradermal injections of the patient's own serum in the

treatment of hay fever. If the antigens concerned in the production of allergic symptoms are circulating in the blood they should no doubt be eliminated through the kidneys as well as through other channels. Duncan^{25, 26} in 1912 and 1914 advocated the oral administration of the patient's own urine in certain diseases, basing his treatment upon the belief that certain bacterial and tissue toxic substances were eliminated through the kidneys and that ingestion of these would stimulate specific antibody formation. Two cases in which the patients claim to have been relieved from asthmatic paroxysms by drinking their own urine have come to our attention. While desensitization by the oral route is of doubtful value it is of interest to note that Thommen²⁷ believes he has induced relief in a case of hay fever following the oral administration of ragweed pollen in large doses.

The work of Oriel and Barber¹⁵ demonstrates quite conclusively that the antigenic substances which they have recovered from the urine of allergic patients are specifically related to the antigens primarily responsible for the symptoms. Proteose obtained from a case of serum sickness will stimulate wheal formation when injected intradermally in other individuals known to be sensitive to horse serum. They showed further that the proteose from a case of serum sickness would induce asthma when administered subcutaneously in rather large dosage to a "horse-asthmatic." By the use of the Prausnitz-Kustner reaction Barber and Oriel advance further evidence as to the specific nature of the urinary proteose. Serum

from an individual suffering from serum sickness was injected intradermally at two points in a normal individual. Twenty-four hours later proteose prepared from this case of serum sickness was injected intradermally in one of these areas and proteose prepared from a non-serum sensitive individual was similarly injected in the other. A positive reaction as evidenced by wheal formation appeared in the area injected with serum proteose, no reaction occurring in the second or control area. Oriel¹⁴ using the uterus of a guinea pig which he had sensitized with proteose prepared from a milk sensitive patient observed a strong contraction when milk was added to the perfusing fluid in which the uterus was suspended. Similar results were obtained with a uterus sensitized to milk when the proteose was added to the perfusate.

Many of our observations substantiate these findings. One of our patients presented a violent generalized urticaria following the ingestion of a breakfast food containing flax to which she was found to be sensitive. Proteose was prepared from this patient and tested in another patient known to be flax sensitive. A marked local reaction was obtained. Similar reactions were observed when proteose prepared from a case of serum sickness was tested intradermally in serum sensitive individuals. Two hay fever patients each sensitive to the same pollen will respond with positive intradermal tests to each other's proteose.

The significance and exact origin of this urinary antigenic substance is somewhat problematical. Early workers in the field of immunology recog-

nized the possibility that the symptoms of anaphylaxis might be due to products of parenteral digestion or to products formed as a result of the reaction between the primary antigen and the sensitized tissue. Oriel and Barber¹⁵ after reviewing the experimental work of Lewis, Dale and Manwaring, consider that the urinary proteoses which they have found in all probability consist of these "secondary antigens" which are formed as a result of the interaction between the "primary antigens" and the sensitized tissues of the body.

Regardless of the origin of this antigenic substance found in the urine of allergic patients it is evident from the results reported by the original investigators and also from the hay fever cases reported in this paper that desensitization with homologous urinary proteose is of great practical importance. Many cases of allergy are seen in which the primary antigen is obscure and if a patient can be desensitized with his own proteose much is to be gained. Other cases occur in which it is probable that the primary antigen is derived from metabolic processes, or as the result of low grade infections, and in such cases it is difficult to desensitize a patient by the usual methods.

It must be understood that further investigation and experience with this urinary substance is necessary in order to arrive at a better understanding regarding its origin, significance and technique of application. We feel that the work of Oriel and Barber is of great importance in that it may open the way toward the solution of many problems of an allergic nature.

CONCLUSIONS

The literature regarding the antigenic properties and uses of proteoses is briefly reviewed laying particular stress upon the work of Oriel and Barber

Urinary proteose was prepared according to the original methods of these investigators and the intradermal and therapeutic response determined in twelve cases of seasonal hay fever. All cases gave positive intradermal reactions to their respective proteoses and improved after desensitization.

These cases are discussed at length regarding the clinical results obtained and also regarding the contention that

a given proteose is specifically related to a given antigen. The work of Oriel and Barber is briefly discussed relative to this point and confirmatory observations by us are indicated.

The probable origin and significance of this urinary substance is also mentioned in an effort to point out the important rôle which it may play in the future study and treatment of allergic diseases.

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REFERENCES

- ¹FINK, E B The antigenic properties of proteoses, Jr Inf Dis, 1919, xxv, 97-123
- ²AULD, A G Preliminary note on a new treatment of bronchial asthma, Brit Med Jr, 1917, i, 580-581
- ³AULD, A G Observations on peptone immunisation in asthma and other allergies, Lancet, 1923, i, 790-795
- ⁴MILNER, J L, and RAULSTON, B O Treatment of migraine with peptone, Jr Am Med Assoc, 1923, lxxx, 1894-1896
- ⁵PETROW, H, and WITTKOWSKA, E Zur Desensibilisierungstherapie des Asthma bronchiale, Klin Woch, 1930, ix, 1712-1715
- ⁶URBACH, E Orale Desensibilisierung alimentär-idiosynkrasischer Dermatosen mittels artspezifischer Peptone, Klin Woch, 1930, ix, 2046-2049
- ⁷UHRICH, F Zur Desensibilisierung allergischer Krankheiten durch Peptonspritzungen, Klin Woch, 1930, ix, 2039-2040
- ⁸BROWN, G T The treatment of urticaria and angioneurotic edema, Ann Int Med, 1929, iii, 591-603
- ⁹VALLÉE-RAVET, L, and GIBOUD, P Des réactions recréées sur le rhume des foies, Presse méd, 1928, i, 151-155
- ¹⁰WELLS, H G Chemical Pathology, 5th ed, W B Saunders Co, 1925, p 659
- ¹¹BARBER, H W, and ORIEL, G H A clinical and biochemical study of allergy, Lancet, 1928, ii, 1064-1070
- ¹²ORIEL, G H A preliminary note on the occurrence of a substance of a proteose nature in the urine in certain diseases, Guy's Hosp Rep, 1929, lxxix, 376-378
- ¹³ORIEL, G H Some observations on the biochemistry of asthma, Guy's Hosp Rep, 1929, lxxix, 480-490
- ¹⁴ORIEL, G H Some observations on pathogenesis of eczema of internal origin and other allergic diseases, Proc Roy Soc Med, 1931, xxiv (Sect Dermat), 55-64
- ¹⁵ORIEL, G H, and BARBER, H W A proteose in the urine excreted in anaphylactic and allergic conditions, Lancet, 1930, ii, 231-237
- ¹⁶DARLEY, W, and WHITEHEAD, R W Studies on urinary proteose, skin reactions and therapeutic response to injections, Proc Soc Exper Biol and Med, 1931, xxviii, 668-669
- ¹⁷DARLEY, W, and WHITEHEAD, R W Proteose obtained from urine of allergic patient, skin reactions and thera-

- peutic applications, *Colorado Med*, 1931, xxviii, 293-296
- ¹⁸ALEXANDER, H L An evaluation of the skin test in allergy, *ANN INT MED*, 1931, v, 52-56
- ¹⁹COCA, A F, WALZER, M, and THOMMEN, A A Asthma and hay fever, in theory and practice, Charles C Thomas, 1931, part 3, p 769
- ²⁰AULD, A G Nonspecific treatment of asthma, *Lancet*, 1931, i, 804-806
- ²¹KAHN, M H, and EMSHEIMER, H W Autogenous defibrinated blood in the treatment of bronchial asthma, *Arch Int Med*, 1916, xviii, 445-454
- ²²HENSKEL, A C The treatment of bronchial asthma with autogenous defibrinated blood, Jr *Missouri Med Assoc*, 1921, xviii, 431-435
- ²³GHOSAL, J N Angioneurotic edema, *Indian Med Gazette*, 1931, lxi, 510
- ²⁴FLANDIN, C Le rhume des foins, *Bull méd*, Paris, 1928, xlii, 665
- ²⁵DUNCAN, C H Autotherapy, *N Y Med Jr*, 1912, xcvi, 1278-1283
- ²⁶DUNCAN, C H Autotherapy of urine and sea plasma, *Therap Rec*, 1914, ix, 38-42
- ²⁷COCA, A F, WALZER, M, and THOMMEN, A A Loc cit ¹⁹, p 764

The Successful Treatment of Hay Fever and Pollen Asthma

By ALEXANDER STERLING, M D , *Philadelphia, Pa*

DESENSITIZATION with pollen extracts for hay fever patients has been in vogue for the last fifteen years. The method originally conceived by Walker, Cooke, and others has not changed a great deal over that period and even now the treatment by the general practitioner of patients with hay fever and hay fever and asthma consists of a series of fifteen injections at weekly intervals. There has been so much controversy regarding beginning and protective doses, types of doses, etc., that there scarcely seems a way for the general practitioner to determine preference for any of the so-called "treatment sets" now on the market. Of these various "sets", there are many which are similar in contents and which are alike in that they are successful in only twenty per cent of all hay fever patients. Physicians and patients alike have informed me that pollen desensitization is of no avail, because they have tried this, that, and the other manufactured product with no success. The complainings have reached the stage where the practitioner says that there is no relief for hay fever, and at times insists that these "treatment sets" cause an even worse condition in the patient.

It is unfortunate that from the very

beginning of pollen therapy there was no standard for the preparation of pollen extracts nor any standard treatment adopted by allergic societies and recommended to pharmaceutical houses. The conditions existing, which I would like to explain and attempt to solve, are several.

First, there is no standardization in product of the various numerous pollen extracts now available. The pollen extracts are obtained from menstrums of saline, alcoholic saline, glycerol saline, and other types. All sorts of percentage compositions are resorted to in the make-up of the menstrums. I have experimented with various types and have found that if the pollen is extracted from a menstrum of fifty per cent glycerin and fifty per cent buffered salt solution, nearly perfect results are obtainable. All menstrums which do not contain glycerin are unstable. They are potent only when freshly prepared, when constantly kept on ice, or when received from the manufacturers. They quickly lose potency with changes in temperature or after certain intervals of time. These results are not dependent entirely upon the extraction liquid. Another fault existing in the makeup of the various pollen extract is in the standard of measurement. The various units used

to grade the strengths of pollen extracts range from protein nitrogen units (each unit equivalent to 0.001 mg of protein nitrogen) to pollen grain units (the amount of pollen grain extract from 0.001 mg of pollen)

Second and most important, no preparation on the market has sufficient material made up in a proper way for correct desensitization and successful results. It would be rather illuminating at this time to examine several of the products now in common usage.

Product number 1 contains three 4 c.c. vials of extracts of various pollens of particular groups. The three vials contain various proportions of pollen grains per cubic centimeter and furnish sufficient material for the usual fifteen dose treatment. The course of injection treatment is so constituted that the dosage begins with two pollen units, and the protective dose furnished is 1200 pollen grain units. A higher concentration is available in a 4 c.c. vial containing 2000 pollen grain units per cubic centimeter.

Product number 2 is a mixture of various pollen extracts standardized to contain about 2000 pollen grain units, or 500 protein nitrogen units per c.c. The extract is supplied in 5 c.c. vials and it is suggested that the practitioner adopt a graduated dosage beginning with 1/20 c.c., and progressing in either twentieths or tenths of a c.c. so as to obtain thirteen injections from the 5 c.c. vial. A fifteen dose treatment package of graded doses proceeding from 100 pollen grain units to the protective dose of 4000 pollen grain units is also manufactured. Each dose is in a separate syringe.

Product number 3 is standardized

according to the "protein nitrogen unit." This product is in two 5 c.c. vials; the starting dose is 5 units and the highest dose is 100 units. Sixteen doses are offered for injections and if larger doses are required another vial is offered, the highest dose being 250 protein nitrogen units.

Product number 4 contains four 3 c.c. vials and one 1 c.c. vial. It is an alcoholic saline pollen extract ranging in dilutions (volumetric method) from 1/10,000 to 1/100. The highest dose suggested is 5 minims of 1/100 dilution. Similar products are manufactured by other well known firms. They are all proponents of "treatment sets."

The doses, as can be seen from the above, range from between 2 pollen grain units and 100 pollen grain units as the lower level, to the apparently highest protective doses of from 1000 to 4000 pollen grain units. In a single exceptional case only does the highest protective dose reach anywhere near the correct figure of 10,000 pollen grain units. The highest dose suggested by the pharmaceutical houses is between 3 and 5 minims of a one per cent solution (or 0.025 or 0.030 nitrogen units), which they consider sufficiently protective.

For several years I have had five groups of 10 patients, each of whom I have treated with various advertised treatment sets. Only twenty per cent of these patients were benefited. Furthermore, only those who had hay fever were benefited. Those who had hay fever and asthma were not relieved by these preparations. Not until I began to use a three per cent concentrated pollen extract in various dilutions did I achieve nearly perfect re-

sults in 90 to 95 per cent of patients

Standardization of pollen extract, as mentioned above, by the protein nitrogen unit does not hold good for the reason that it has been proved by investigators that the carbohydrate fraction of pollen is just as responsible in the production of hay fever and asthma symptoms as the nitrogen fraction. I therefore have selected the pollen grain unit which is the quantity of pollen weight per unit of diluent. For example, 3 gms of pure washed pollen to 100 c c of glycerol and buffered salt solution is passed through a Berkefeld filter after one or two days standing. This extract contains approximately 30,000 to 32,000 pollen grain units per 1 c c which is a three per cent concentrated pollen extract. The reason why I limit myself to a three per cent pollen extract is that it has been demonstrated by many investigators that a three per cent concentrated pollen extract is equivalent to a saturated solution of pollen.

I use the following *dilutions*

Dilution No 1 Five minims of 3 per cent concentrated pollen glycerol extract to 10 c c diluent. Each minim containing 57 pollen grain units (The diluent that I favor is a sterile physiological salt solution containing 0.2 or 0.3 per cent carbolic acid). I find from my experience that any solution which contains from 30 to 50 per cent glycerol is very painful when injected.

Dilution No 2 Ten minims of 3 per cent concentrated pollen glycerol extract to 10 c c diluent. Each minim containing 114 pollen grain units.

Dilution No 3. Twenty minims of a 3 per cent concentrated pollen glycerol extract to 10 c c diluent. Each

minim containing 228 pollen grain units.

Dilution No 4. Forty minims of 3 per cent concentrated pollen glycerol extract to 10 c c diluent. Each minim containing 456 pollen grain units.

Dilution No 5 Eighty minims (5 c c) of 3 per cent concentrated pollen glycerol extract to 10 c c diluent. Each minim containing 912 pollen grain units.

Treatment. The most important factor in this work is to begin treatment with a dose small enough to give a local reaction not exceeding one inch (from 2 to 2.5 cms) in diameter. Quite often I find that the 2 minim dose of dilution 1 gives quite a large local reaction, sometimes accompanied by a constitutional reaction. In those cases I am compelled to make another dilution (1 A) containing about 2.5 minims of 3 per cent concentrated pollen glycerol extract to 10 c c diluent. This dilution contains about 28 pollen grain units. The first injection may even go down as low as 14 pollen grain units, in order to obtain a local reaction not exceeding one inch in diameter. It is here, in the beginning of treatment, that the only difference between a strongly sensitive and a weakly sensitive patient's dosage occurs. There is no necessity for complicating the treatment with various classifications of sensitivity A, B, C, and D as it is being practiced in some clinics. The protection doses in all cases are approximately the same.

Having obtained the starting dose (that which produces a local reaction not exceeding one inch in diameter) whether it be in solution 1, 1A, or 1B, the next dosage is four minims of that

solution The dosage of dilutions 1, 2, 3, and 4, is gradually increased consecutively to 4, 6, 8, 10 and 12 minims When changing from one solution to the next the first dose of the next vial may be 4, 5, or 6 minims The reason why I start with four minims of the following dilutions (which is a repetition of the dose) is to prevent a reaction from too large a dose from the next vial in case of difference or freshness of the pollen extract When the dose reaches solution 5, (which is approximately 1 per cent concentrated pollen extract), injections increase 1 minim daily until 12 to 15 minims are reached before the pollination periods of the respective seasons That, in the majority of cases, furnishes the highest protective dose

A suggestion of all pharmaceutical houses is that injections should cease with the beginning of the season. That is faulty The patient should receive injections of the highest protective dose (from 12 to 15 minims of 1 per cent pollen extract) throughout the season at least once a week In severe seasons, at the slightest appearance of mild symptoms my patients receive injections every day for a few days until 18 to 20 minims of solution 5 are given That, in some cases is the highest protective dose In the severest cases I find that the protective dose is about 15,000 pollen grain units In this way through these various procedures I have been able to attain perfect results in 90 to 95 per cent of patients no matter how severe the previous pollen intoxications

Discussion The shortcomings of the 15 dose treatment sets on the market are as follows

a The protection dose is in none of the sets sufficiently high for a complete relief

b The series of injections should not stop at the dose which gives the reaction but should either repeat or go back to a weaker injection In case of a constitutional reaction somewhere along the line the dose cannot be reduced or repeated on account of lack of material in the "treatment sets"

c Instructions to the general practitioner by most pharmaceutical houses state that the last dose (15th) should be given at or about the beginning of the respective pollination periods This conveys the impression to the physician and in turn to the patient that they are going to stay well and protected for the 6 to 8 weeks of the season, which is absolutely not justifiable Only one out of 15 or 20 may remain protected All others must have the maximum dose repeated every week for the season if protection is to be maintained

d The advice given by various clinics and certain manufacturers to increase the dose in the course of desensitization by 100 per cent or 50 per cent, is entirely wrong A patient can never be favorably desensitized to a higher strength by consistent doubling of the strength of the injection

In regard to reactions there are several considerations The patient must be kept in the office for at least one-half hour following the injection so that in case of any reaction from 3 to 5 minims of adrenalin may be administered

After a reaction the following day's injection should be 2 minims below the dose which provoked the reac-

vious reaction The dosage should gradually be worked up by 1 minim increases and after the previous reaction stage has been passed, increase may again be made by 2 minims

Patients receiving dilution 5 should never be increased by more than 1 minim at a time I have seen patients give violent reactions to, let us say, 7 minims of dilution 5 The following day they were given 5 minims of dilution 5, followed by a 1 minim increase every day, until receiving 10, 12, and even 15 minims without the slightest reaction The presence of a reaction does not mean that the patient is protected On the other hand, it merely reveals that the patient is not yet prepared for that particular dose and he must be worked up to it again by daily injections

Occasionally one finds patients whom you cannot work up to the protection dose Such patients occur in a proportion of 1 in about 15 or 20 In these cases increase of dose is halted and the highest dose the patient can receive without untoward reaction, is injected In this type of patient we achieve 80 per cent favorable results, and even though the protective dose has not been reached, the symptoms, if any, will be mild. It has been my experience that such patients do reach their protective dose during the second year of treatment

It is important to note that

1. There are from 20 to 25 injections given before there is any possibility of reaching dilution 5

- 2 The time interval is daily or even twice daily in the milder dilutions All injections are to be given intradermally, if possible

- 3 There are about 15 to 20 injections of dilution 5 necessary as a protective dose to be reached before the beginning of pollination of the summer (grass) and fall (weeds, etc) seasons. For the spring (tree season) 12 to 15 minims of dilution 4 may be sufficient for the protection dose

Patients receiving 15 to 20 minims of dilution 5 (equivalent to from 12,000 to 15,000 pollen grain units) are protected from any amount of pollen in the air, no matter how severely they have suffered in previous years, provided this dose is repeated once a week throughout the season

It would therefore be necessary for the general practitioner in order to successfully treat a case of hay fever or hay fever and asthma, to buy in the open market 15 to 20 c c of a 3 per cent concentrated glycerol-saline pollen extract for the respective season which is indicated by preliminary testing, and to obtain from a local laboratory five or more vials of sterile 10 c c physiological salt solution which would enable him to make his own dilutions

Continuation Treatment I have used the "continuation treatment" for the past four years This means to keep the patient under the maximum protective dose of pollen extract injected at the longest time interval throughout the year without inducing a reaction It is practical and desirable in the class of patients who can stand the maximum protective dose repeated every three, four, or five weeks without a reaction In about 5 to 10 per cent of patients the longest time interval, unfortunately, is not more than one week or ten days Every time the maximum dose is injected every ten days or two

weeks the patients get a reaction The maximum dose has to be constantly reduced by 1 or 2 minims so that at the following season the patient should have daily injections for two or three weeks to work him up to the highest protective dose Under these circumstances there is not much gained by the continuation method of treatment in this type of patient

EXAMPLE OF PROCEDURE IN TREATMENT

Dilution 1A Each minim contains 28 Pollen Grain Units

2 minims

4

6

8

10

12

Dilution 1 Each minim contains about 57

Pollen Grain Units

4

6

8

10

12

Dilution 2 Each minim contains about 114
Pollen Grain Units

4

6

8

10

12

Dilution 3 Each minim contains about 228
Pollen Grain Units

4

6

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12

Dilution 4 Each minim contains about 456
Pollen Grain Units

4

6

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12

Dilution 5 Each minim contains about 912
Pollen Grain Units

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Cardiac Failure

Report of a Case of Cardiac Decompensation of Fourteen Months Duration

By EDWARD J STIEGLITZ, M S, M D, F A C P, *Chicago, Ill*

IT is most unusual for cardiac decompensation with severe edema to persist for as long as fourteen months. Cardiac failure and its associated phenomena have been repeatedly described and discussed, but the present instance permitted of long and careful study throughout the latter course of the decompensation, and revealed a number of most significant phenomena which warrant discussion.

REPORT OF CASE

The patient, a widow with one child, was first seen June 25, 1928, at which time she was 55 years old. The chief complaint was marked dyspnea, occurring particularly upon exertion, but noticeable even at rest or when talking. Pedal edema was also noted. A similar period of breathlessness and edema had occurred in 1924. The past history revealed frequent attacks of tonsillitis as a girl and considerable intoxication during the one pregnancy in 1898. The climacteric had been very abrupt in 1923. Her habits were good with the exception of a rather too liberal use of condiments. Exercise had long been extremely limited, both because of the low threshold of dyspnea and because of her obesity (her weight ranged about 200 lb., although the patient was but 4 ft. 11 in. in height). A lifelong history of migraine with typical cephalalgia and scotomata was elicited. The family history was significant in as much as both parents, one sister and two brothers had all died of

cardiac failure, probably of the hypertensive type

Physical examination revealed a short obese elderly lady with moderately ashen subcyanotic facies. There were moist and crackling râles in the pulmonary bases. The left border of the area of cardiac dullness extended 12 cm to the left, the right border was substernal. The second aortic sound was ringing in tone and accentuated, a very soft systolic aortic murmur was noted. The pulse was 98 at rest. The arterial tension was determined at 210/125 at rest, but fell to 180/120 upon minor exertion and to 152/100 upon the inhalation of amyl nitrite.¹ There was some pedal edema, dyspnea was marked upon very minor effort. The urine was normal.

The diagnostic summary made at this time noted the following

- 1 Arterial hypertension with moderate arteriolar sclerosis
- Probable etiologic factors
 - 1 Hereditary influences
 - 2 Obesity
 - 3 Intoxication of pregnancy (1898)
 - 4 Frequent tonsillitis
 - 5 Oral sepsis
 - 6 Abuse of condiments
- 2 Hypertensive heart disease,
Early decompensation
- 3 Obesity
- 4 Former migraine
- 5 Probable alveolar infection

The patient was advised to rest, stop the use of condiments and meat extractives have roentgenograms made of her teeth take dried digitalis leaves, gr iss, t i d. and bismuth subnitrate, gr x, tid 3,4,5

On July 2, 1928, the renal concentration test revealed a maximum specific gravity of 1024, 30 mg of albumin per hundred c.c., a few casts, no sugar. The dyspnea was much improved, the arterial tension was 200/90. On July 18 a large dental abscess was demonstrated. The dyspnea had disappeared and the arterial tension was 184/85. By August 18 the arterial tension had fallen to 178/82, the pulse to 80. When seen September 17 the patient had had a severe shock as a result of a holdup and burglary. Since then the dyspnea had returned, the arterial tension had risen to 220/104. With similar digitalis therapy and continuation of the bismuth subnitrate, on September 26 the pulse was 86, dyspnea almost gone and the arterial tension 180/88. It was noted in October that she felt much calmer and less unstable emotionally, the arterial tension was then 162/84, and in November, 172/93. The abscessed tooth had as yet not been attended to. The dosage of bismuth subnitrate was reduced to gr. x twice daily in October.⁶ During 1929 the patient felt quite well, complained only of dyspnea and some precordial pain upon exertion, during this year the arterial tension was observed to be 165/85, 166/90, and 175/90. The immediate outlook for the patient was rather encouraging.

On January 17, 1930, the patient was seen at home. She had been acutely decompensated with very marked pedal edema, severe breathlessness even at rest, orthopnea and cough for 2 or 3 weeks. The cardiac failure had been induced by a coryza with cough. At this time the pulse was totally irregular with almost alternating extra systoles and ranging about 120 in rate. The arterial tension was 170/100. From then on for 14 months it was a continuous daily struggle with the decompensation with a multitude of therapeutic agents, some of known and others of undemonstrated value. Certain of the clinical phenomena such as variation in weight, pulse, arterial tension, nausea and dyspnea are best illustrated graphically (figure 2).

The termination of this extraordinarily prolonged congestive cardiac failure was unusual—a sudden occlusion of the left femoral

artery caused gangrene of the left leg and such profound intoxication that the myocardium failed rapidly. Just prior to this fatal accident the patient was in better condition than at any time previously for a year. It is notable that throughout the prolonged decompensation with edema the urine was essentially normal. On March 9, 1931, the patient complained of sudden severe deep pain in both legs. This gradually became localized in the left leg and was not relieved by hot or cold packs or moderate sedatives. On March 10 it became necessary to administer 1/6th gr. of morphine sulphate, the left leg was hot, of a blotchy red, and very tender. A cellulitis in the edematous tissue was suspected. By evening the pulse had risen to 110, the temperature to 101.4° F. On March 11 the arterial tension had fallen to 125/70, the pulse was 120, temperature, 102°, the patient was semicomatose, very cyanotic and the leg revealed large blotchy areas of deep cyanosis extending up to a sharp border at mid-thigh. By evening of the next day these blotchy areas had formed huge watery blebs which drained bloody serum profusely. At 7:30 P.M. on March 12 the patient was in deep coma and extremely cyanotic, the pupils were large but rigid, respirations were 44 per minute, temperature, 102° F., pulse, 110. At 9 P.M. the respirations were 48, pulse 114, arterial tension, 112/40, at 11 P.M. respirations were 50 and more labored, pulse 120, arterial tension, 104/35, at 12 midnight the tension had fallen to 98/32 and to 88/26 at 1 A.M. when the pulse was approximately 140 and totally irregular. The patient died at 1:42 A.M.

Necropsy. Only the essential observations will be recorded. The heart was very large and firm with most of the increase in size resulting from marked hypertrophy of the left ventricle. The right heart and the mitral valves were normal. The aortic valve was markedly stenotic and the cusps distorted. The valve ring was incomplete. Areas of calcification in the valve leaflets were quite extensive. The ascending portion and the arch of the aorta were smooth and glistening without defects. Several coronary vessels upon being opened revealed

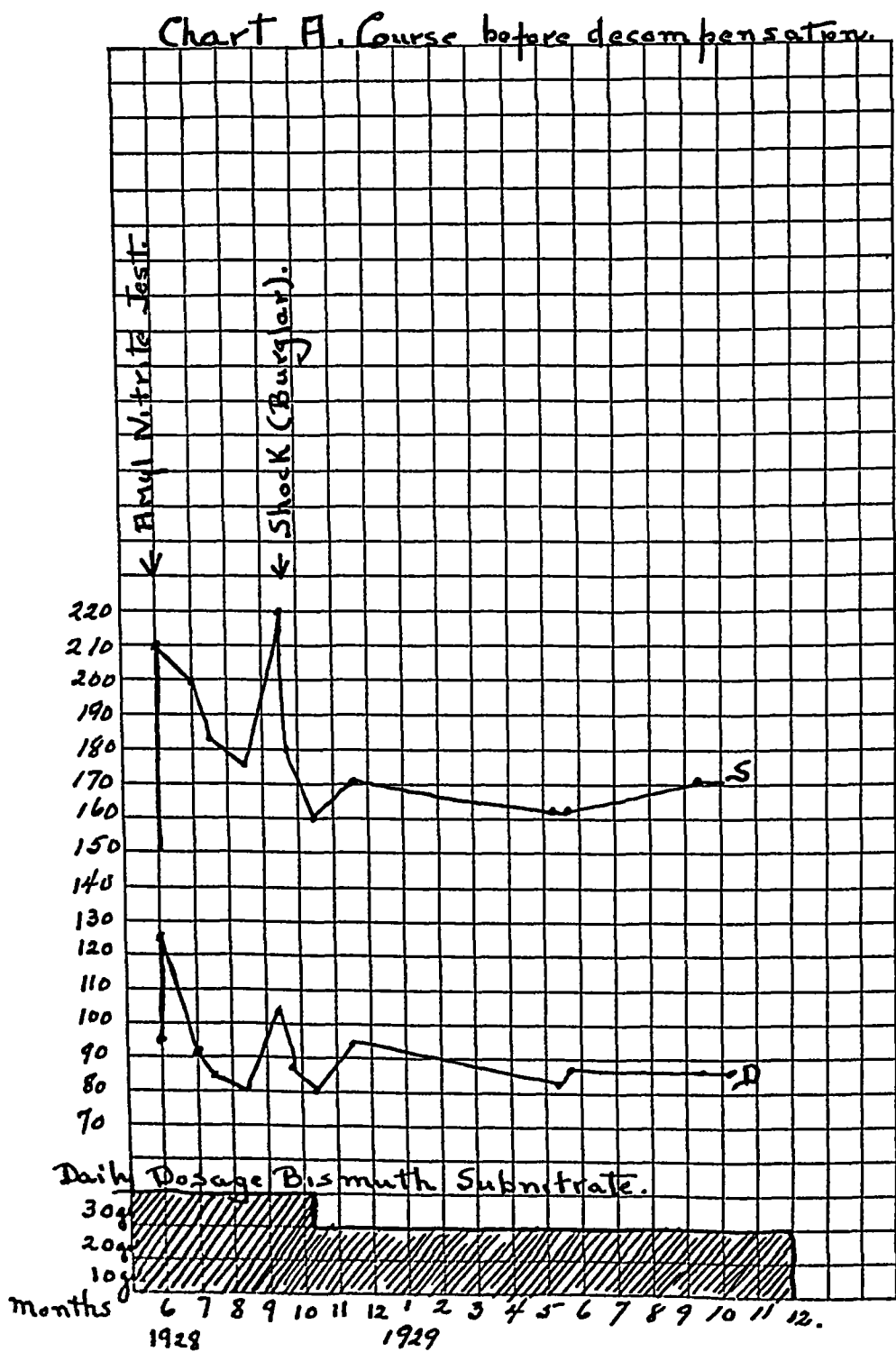


FIG 1 Chart A Course of the arterial tension under therapy with bismuth subnitrate prior to cardiac decompensation

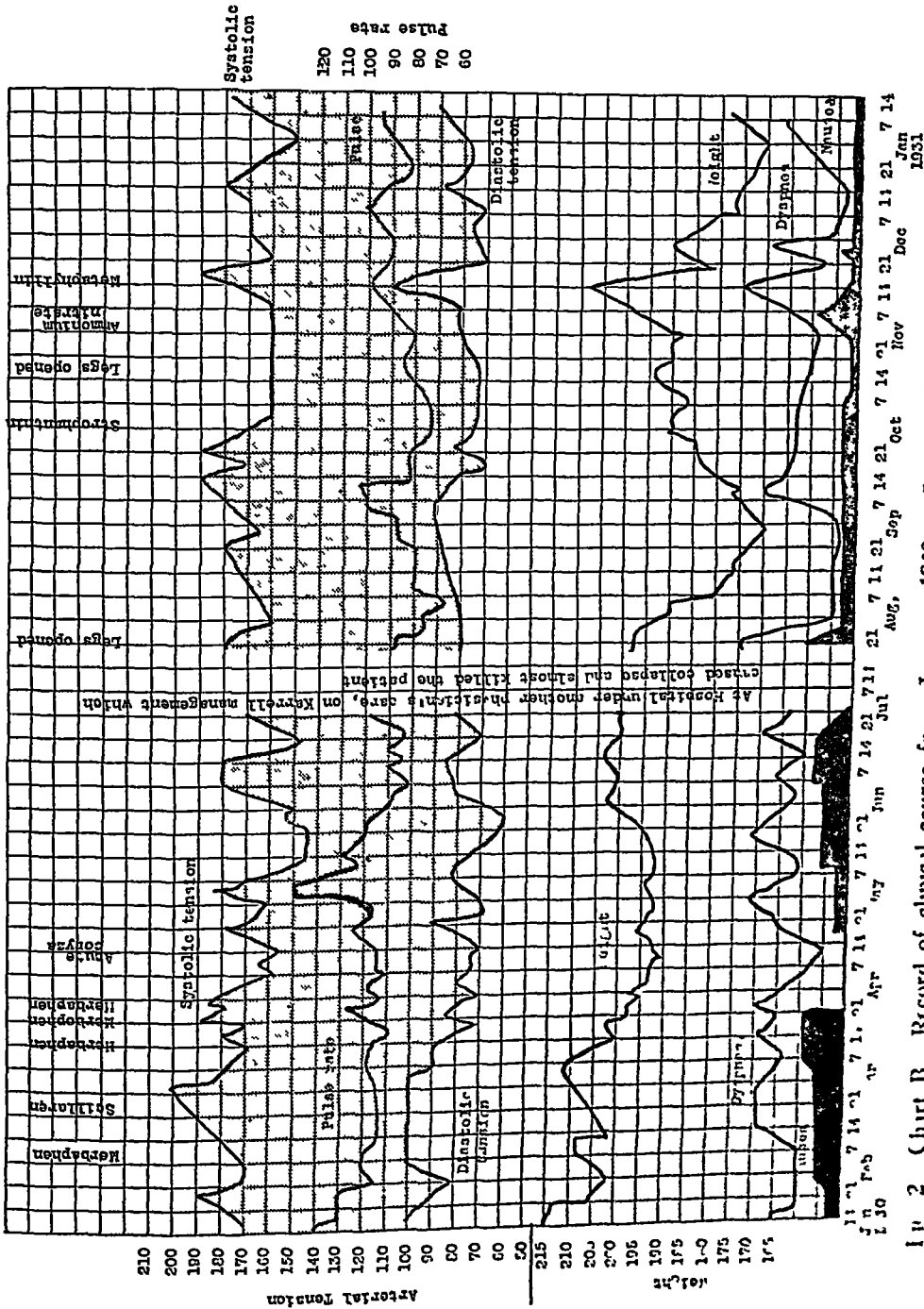


Fig. 2 Chart B. Record of clinical course from January, 1930, to January, 1931. The average arterial tension, pulse and weight are recorded. The pulse pressure is represented by the shaded portion of the chart between the systolic and diastolic tensions. The degrees of dyspnea and of nausea are indicated along the base of the chart. Medication is recorded very incompletely, throughout this period digitalis and appropriate sedatives were administered and continued. During the first two weeks of July the patient was under another physician's care and on Kerrall management. The course from January to March, 1931, is not included.

moderate sclerotic lesions. The pericardium was normal, as was the endocardium with the exception of the aortic valves.

The kidneys were of normal size, the capsules stripped readily and cut surfaces appeared normal. The liver was hard, pale, and large. Surfaces made by cutting appeared grayish, as though cooked. The spleen also was engorged, somewhat enlarged, and firm. In the left femoral artery a rather fresh thrombus occluded the lumen at about the upper third of the leg.

Microscopic Findings. Throughout the tissues studied, marked and extensive arteriolar changes were seen. In the kidneys, heart and spleen, these were most marked. There was extensive thickening of the media, hypertrophy of the spiral smooth muscle fibers and some fibrotic changes in the intima of the arterioles and pre-capillary arterioles. Some medial thickening of the vasa vasorum of the aortic adventitia was noted.

The renal parenchymal structures were essentially normal, both the tubules and glomeruli failed to reveal any appreciable damage despite the very prolonged severe edema.

The hepatic cellular strands were widely separated by edema, intense fatty vacuolization of the hepatic cells existed, especially in the central portion of the lobules. Hepatic fatty degeneration is characteristic of prolonged anoxemia. The Kupffer cells were more prominent than is usual. The portal canals and biliary ducts were essentially normal.

The intimal and medial portions of the aortic wall were normal. Arteriolar sclerotic changes were noted in the vasa of the adventitia. The elastic tissue was not disturbed, nor was the tunica elastica intima abnormal.

The heart muscle stained very poorly with phosphotungstic acid. The fibers were somewhat shortened and thicker than usual. The normal striations, however, were not appreciably altered. The nuclei of the cardiac muscle were pale, a few pycnotic nuclei were noted. The usual spindle shaped accumulations of sarcoplasm about the nuclei were not demonstrated. No evidences of toxic or inflammatory lesions were found. Both the smallest and larger coronary ar-

teries seen on section revealed markedly thickened and hypertrophied medial layers—the medial muscular hypertrophy of hypertensive disease.

The aortic valve revealed extensive heavy calcification, chiefly at the base of the valve. The endothelium of the valve margin and sides was normally intact. Calcification, partially stratified, appeared along the valvular attachment, being densest along the center of the valve leaflet and in two bands below the subendothelial reticulum. A vasa vasorum sectioned at the valve base revealed marked sclerotic narrowing with intimal proliferation. Such findings are in agreement with previous observations⁷ which indicate that such aortic valve calcification may be largely due to ischemia induced by impaired vascular supply.

COMMENT

The above brief resumé of the course of this unusually prolonged instance of cardiac failure merely outlines the sequence of events and does not touch upon the profound significance of a number of phenomena and the related therapeutic problems.

The comparative value of various therapeutic agents was demonstrable because of the opportunity for prolonged observation. Certain aspects of the complex problem of edema of circulatory origin are worthy of emphasis. The behavior of the arterial tension, and particularly the pulse pressure, deserves consideration. The most unusual termination by thrombosis of a peripheral artery in an edematous extremity warrants recording.

At the very onset of the cardiac decompensation it was made clear that medication intended to reach and to affect the heart had to be administered in such a manner that delivery to the site of action was assured; medication was by intravenous injection. Digitalis



FIG 3 Kidney, magnified 77.5 diameters, hematoxylin and eosin stain. The tubular and glomerular structures are essentially normal. The medium sized artery shown on the right reveals extensive thickening of the media and some intimal proliferation.

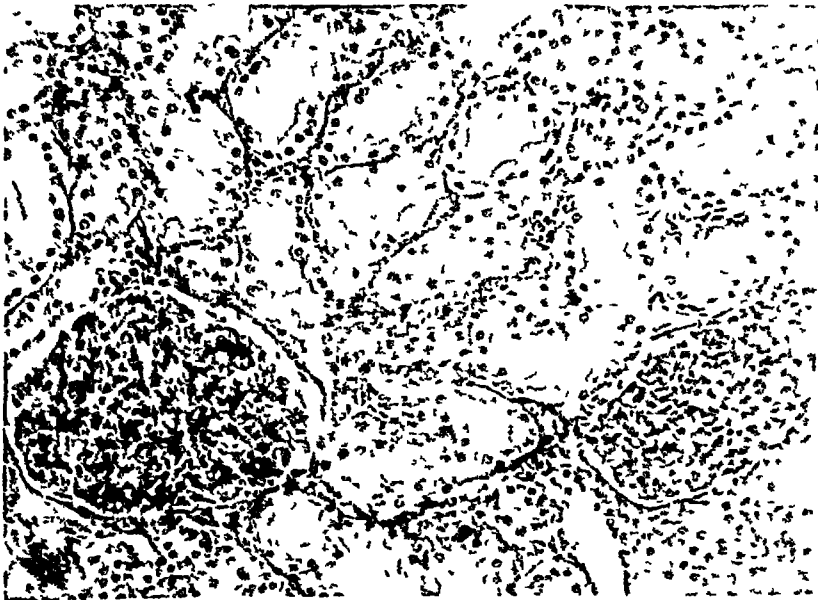


FIG 4 Kidney, magnified 154 diameters, hematoxylin and eosin stain. The normal appearance of the tubules and glomeruli are well demonstrated here, there is some edema of the stroma.



FIG 5 Liver, magnified 232.5 diameters, phosphotungstic acid, hematoxylin stain. Fatty degeneration of the parenchymal hepatic cells. Increase in size and depth of stain of the Kupfer cells of the sinusoids, notable in the center of the field.

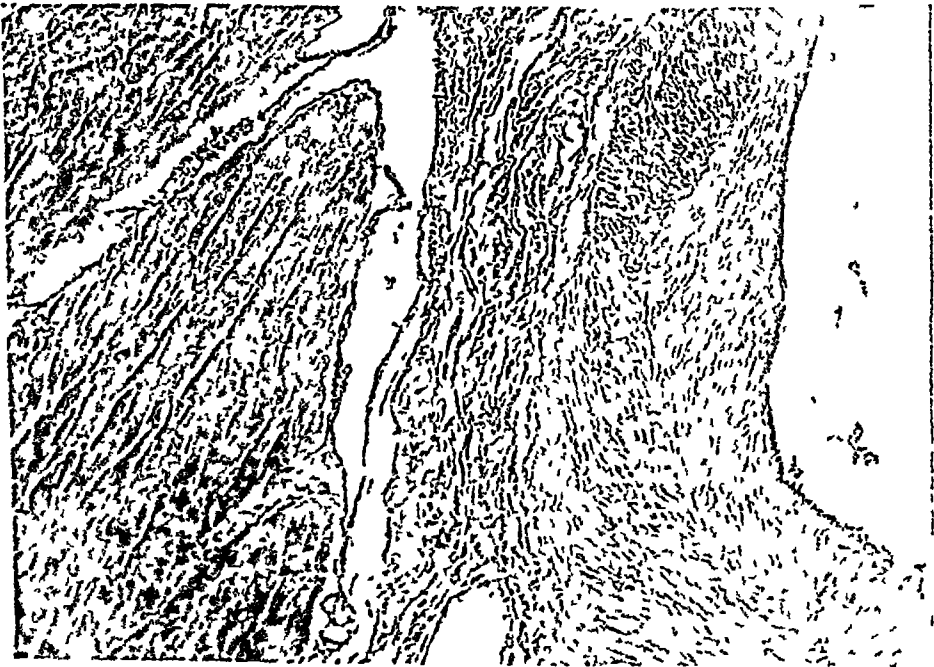


FIG 6 The myocardium, pericardium and part of a coronary artery, magnified 77.5 diameters, hematoxylin and eosin stain. Thickening of the medial and intimal coats of the arterial wall is visible.

administered by mouth failed to have any effect upon the pulse rate early in the course of decompensation when there was extensive intra-abdominal edema and ascites and when the edema was increasing. It must be realized that in the presence of extensive edema the alimentary absorption of digitalis, or any other drug is greatly interfered with^{8, p. 182}. The gastro-intestinal tract is edematous, as are the other tissues, and apparently most of the drug is retained in the edematous tissue^{8,9}. Subcutaneous administration into edematous tissue is similarly inadequate^{10,11}. It is necessary that digitalis, and similar acting principles actually be delivered to the heart,¹² the site of action. Digitalis, although strengthening the force of cardiac systole, does not cause a rise in arterial tension¹³. The diastolic pressure is usually lowered by the improved efficiency of the circulation, which produces increased renal secretory efficiency and greater elimination of toxic waste. Improvement in the circulatory efficiency likewise results in more effective cerebral circulation. As the prime purpose of digitalis medication is to slow the pulse,¹⁴ it should be administered in adequate dosage. The danger of cumulative effects of digitalis has been exaggerated¹⁵. Most patients suffer far more from inadequate than from excessive administration^{16,17}.

Toxic effects of overdosage of digitalis are usually first manifest as nausea and vomiting, later diarrhea, cephalalgia and disturbances of vision²⁸ may appear, with heart block occurring in instances of marked overdosage¹⁸. The nausea, vomiting and diarrhea have been attributed to reflex action

from the heart, not to direct gastro-intestinal irritation^{19,20,21}. The secondary toxic effects of squill or strophanthin are similar. In the present instance of cardiac decompensation it was repeatedly observed that preparations of squill ("Scillaren," Sandoz) created more nausea than did digitalis. Strophanthin, likewise produced more nausea than digitalis. For many months the patient either was distressingly dyspneic because of relatively inadequate digitalization or she was emphatically nauseated. Neither squill nor strophanthin preparations revealed any clinical advantages over digitalis throughout the course of the decompensation.

Because of the marked disadvantage of nausea induced by adequate digitalization, during the last several months of the cardiac decompensation, coramine, a relatively new synthetic cardiac and respiratory stimulant, was given a trial. It was found to be equal to digitalis in effectiveness in maintaining a slower pulse and caused no nausea or gastro-intestinal distress²². Coramine was well tolerated and was efficient in controlling the severe and distressing dyspnea and orthopnea²¹. Coramine is synthetically produced, its chemical composition is pyridine-beta-carbonic acid-diethylamide²⁴. There was no evidence of cumulative effect, nor was there any indication that tolerance to the drug was being acquired²³. Coramine is said not to depress the auriculo-ventricular conductivity as does digitalis⁻⁶.

Not only is it subjectively distressing for the patient to be semi-continuously nauseated, but it is objectively most undesirable because nausea so

greatly interferes with proper nutrition and caloric maintenance. This was repeatedly demonstrated in the present instance whenever nausea and anorexia prevented the patient from taking an adequate diet, the cardiac insufficiency was augmented. It has been emphasized by Smith, Gibson and Ross²⁷ that an adequate glucose intake is essential for recuperation of injured myocardial tissue. For this reason alone it is most important not to aggravate the anorexia of the very sick patient. As it is most illogical to anticipate active reparative rehabilitation of injured tissues under conditions of tissue undernutrition or inadequate oxygen supply, maintenance of an adequate hemoglobin content of the blood is of similar significance.

The behavior of the pulse pressure during this prolonged period of cardiac inadequacy was most instructive. It was noted (see figure 2) that whenever the cardiac efficiency declined there occurred a marked depression of the diastolic tension with a corresponding increase in the pulse pressure. These changes occurred frequently whenever exertion, excitement, transient coryza or excessive fatigue further exhausted the myocardium as evidenced by greater rapidity of the pulse rate, greater dyspnea and gains in weight due to increasing of the edema. It has long been taught²⁸ and correctly, that diminution of the myocardial efficiency results in reduction of the systolic tension and pulse pressure and that such reduction is of ominous prognostic import. The pulse pressure may be considered a rough measure of the stroke volume²⁹ which is ordinarily reduced in cardiac exhaustion.

The pulse pressure usually falls in myocardial exhaustion with tachycardia but is increased in thyrotoxic tachycardia³¹ in proportion to the elevation of the basal metabolic rate, and the increased cardiac volume output. However when the aortic valve is incompetent, the diastolic tension is lowered and the pulse pressure markedly increased. In this patient aggravation of the cardiac inadequacy led to further left ventricular dilation and dilation of the aortic ring. The fact that the aortic valve was calcified was unknown at the time these observations were made. As pointed out by Christian³² calcification of the aortic valves is most frequently undetected clinically when hypertension co-exists. Such aortic valvular calcification is more frequent in males, is very slowly progressive and usually asymptomatic until cardiac decompensation occurs; excessive left ventricular enlargement is the rule as in the present instance. Of 22 cases mentioned by Christian, in 19 the Wassermann was negative; rheumatic infection early in life, as in the present case, is the predominant etiology. Characteristic of such lesions is the asymptomatic course prior to the final and usually brief decompensation.³²

Although diminution in pulse pressure is the usual rule during cardiac decompensation and should serve as a warning of impending disaster³ the reverse may occur because of dilation of the aortic ring and the creation of a state of aortic incompetence. The unwary may be led astray if this is not kept in mind. The presence of murmurs in the aortic area assist but do not make sharply definite a diagnosis.

of aortic regurgitation induced by dilation during cardiac decompensation irregular murmurs all over the precordium both systolic and diastolic in time, obscure their significance. Reduction in diastolic tension *under these conditions* was of ominous prognostic import although the more usual phenomenon is diminution of the systolic arterial tension without great change in the diastolic tension.

Evaluation of the prognosis in the present instance was based upon a number of important considerations, no one factor may be utilized as the sole criterion for prognostication.¹ Of importance are the following factors: (1) history of previous decompensations, (2) the etiologic background of prolonged extensive hypertensive disease, (3) the evidence of aortic insufficiency, (4) the age of the patient, (5) the marked obesity for many years, and (6) the failure of the heart to respond adequately to energetic digitalization. Repeated attacks of cardiac failure reduce the cardiac reserve with each decompensation, some of the surplus or reserve is destroyed with each struggle for returned compensation and a smaller and smaller margin of safety remains. As many as eight instances of cardiac decompensation in the same patient have been observed.⁸

The etiologic background of prolonged and extensive hypertensive disease affected the prognosis adversely. It may be stated as a dictum of clinical experience that in prolonged hypertensive arterial disease myocardial injury exists *a priori*.^{3, p 157} The myocardium is embryonically, anatomically and functionally a specialized portion

of the arterial media, (the site of injury and change in hypertensive disease) and is therefore open to the same sources of injury as initiate the original vascular disease. In addition to this myocardial injury is the factor of fatigue, engendered through excessive and unremitting work in overcoming the high peripheral resistance. Myocardial nutrition is impaired by the malcirculation resultant from coronary arterial disease, such ischemic asphyxial intoxication is a most significant factor. The paroxysms of precordial pain in angina pectoris are apparently the result of cardiac anoxemia.³³ This anoxemia is enhanced by anemia. In the present instance, therefore, it was amply justifiable to assume extensive myocardial injury independent of the valvular disease and myocarditis possibly initiated by the frequent attacks of tonsillitis during the patient's later childhood. The presence of the aortic diastolic murmur, evidencing an aortic regurgitation, further darkened the prognosis. The age of the patient precluded any of the phenomenal recuperative powers of youth and the obesity placed a greatly increased burden upon the faltering myocardium which failed to respond to the intensive digitalization promptly induced at the beginning of the present decompensation. It was primarily in this respect that this third and last attack of cardiac decompensation differed at the onset from the second attack observed 18 months previously. This failure to respond could only indicate one thing: that the myocardium was now most thoroughly exhausted and had almost no reserve to fall back upon.

Aside from the distressing dyspnea

and orthopnea the severe edema or anasarca was the most distressing clinical phenomenon. Throughout the course of the terminal illness the edema was profound, most of the time the patient retained from sixty to eighty pounds of edema fluid. A number of most significant considerations in this condition warrant discussion.

Edema may be defined as any undue accumulation of fluid in the tissues and tissue interstices. For many years it was thought that such accumulation was due to the failure of the kidneys to adequately secrete water. This is not the case, however. The oliguria results from the failure of the renal tissues to receive free water for secretion as urine, the water being held by the tissues. The correction of the earlier erroneous conception, has been due largely to the significant researches of J. Loeb,³⁴ Fischer,³⁵ L. Loeb,³⁶ Aldrich and McClure,^{8,10} Andrews³⁷ and many others. To attempt any comprehensive discussion of edema here is impossible. For our clinical purposes, however, a number of salient conceptions need emphasis. The mechanism of the production of cardiac edema is probably very similar to that of toxic or so-called renal edema; in both instances edema being due to tissue intoxication, alteration of the hydration capacity of the tissue colloids and increased avidity of the tissues for the accumulation and retention of water. Whether these changes be due to circulatory inadequacy as in congestive heart failure, or to intoxication in renal disease is relatively immaterial for our present purpose.

Edema has come to be considered a protective mechanism, possibly an at-

tempt on the part of the tissues to dilute and retain toxic noxa in relatively unimportant structures and thus spare the vital parenchymatous organs. It is notable that the earliest and greatest accumulations of edema fluid are in the skin, extremities and serous cavities, whereas absolutely essential structures such as the heart, kidneys, brain and liver are involved to but a minor degree. In part this may be due to the much greater expansibility of these sites of predilection, in part it may be considered teleologic evidence of the conception that edema is a protective mechanism. Nephritic children become profoundly intoxicated and may develop uremic convulsions if edema is rigidly repressed by deprivation of adequate fluid intake. Convincing evidence makes necessary a change in our original definition of edema in the clinical sense: edema is any undue accumulation of fluid in the tissues or tissue interstices due to changes in the tissues, causing retention of fluid by them and *associated with the accumulation of toxic matter*. Edema fluid is toxic.³⁷ The toxicity of the edema fluid was repeatedly and conspicuously demonstrated in the present instance of congestive heart failure. It is inconceivable that such extensive accumulations of fluid should persist for many months without being laden with toxic metabolic products.

Whenever diuresis was successfully, although temporarily, induced by any method the patient promptly became profoundly intoxicated: the pulse rate rose, dyspnea increased, anorexia, nausea and vomiting became more pronounced, cyanosis deepened and the patient felt intoxicated as though by an

infective process. The more rapidly the edema fluid was shifted from the tissues into the circulation the more marked was the intoxication. This was strikingly manifest during an attempt at edema reduction by Karrell management³⁸ with severe restriction of fluid intake (200 cc milk four times a day and nothing else), undertaken by another physician. This procedure almost killed the patient, the severe restriction of fluids led to such a profound intoxication that the patient became comatose. Only through the prompt introduction of fluids was disaster prevented at that time.

Thus the problem of the treatment of edema is not merely the problem of removing the water of the edema fluid, but consideration of the removal of the very toxic solutes is essential. That these toxic solutes are a real menace is incontestable. Mere transfer of the toxic fluid from the tissue spaces into the circulation is most detrimental, this places the noxa where great damage can be done to the essential parenchymatous structures. On one occasion, Nov. 13, 1930, in the present instance, the patient lost 19 lbs. in 16 hours by diuresis induced by intravenous metaphyllin. This rapid liberation of fluid so profoundly intoxicated the patient that she became semi-comatose and the arterial tension rose to 240/130, causing a transient hemiplegia and aphasia which persisted for 36 to 48 hours.

Such intoxication represents a detriment which far outweighs the benefit of weight reduction through the loss of fluid. It appears immaterial by what medication diuresis is induced, theobromine, theocalcin, metaphyllin, euphyllin, potassium salts, calcium glu-

conate,⁴³ calcium chloride and ammonium nitrate^{39,40} were all used in connection with digitalis, scillaren or strophanthin. Small doses of desiccated thyroid⁴¹ with coramine (no nausea) produced a more persistent and less intoxicating diuresis. Hydrogogue catharsis, as with elaterin, caused marked exhaustion and debility, the loss of fluid was but temporary.

It is of essential importance in the treatment of edema that everything possible be done to assist in cardiac repair and rehabilitation for the primary factor in the causation of such edema is the circulatory failure. Retardation of the exhausting rapid pulse by digitalis or related drugs is of the greatest importance. Adequate nutrition, especially with carbohydrates, is necessary. Oxygen debt may be reduced by the use of an oxygen tent; the diminution in cyanosis and anoxemia is often remarkable.⁴² It is in the advent of these direct cardiac measures being inadequate in reduction of the edema that the other methods of attack must be utilized.

Removal of edema fluid by mechanical means permits of partial relief of the anasarca without liberation of the very toxic debris into the circulation. Should extensive accumulation of fluid occur in the serous cavities, this is readily accomplished by paracentesis or repeated thoracentesis. In the present instance however the edema was dependent, the patient's legs were huge and of almost boardlike hardness up to the mid-thigh. It was only occasionally that evidence of intra-abdominal accumulation of fluid could be elicited, the thorax and upper extremities were at no time edematous. On

two occasions incisions were made in the legs, on either side of the edematous ankles, with most gratifying drainage after the first procedure. After these incisions (about 10 cm long and 3 cm deep into the subcutaneous tissue) had been made, the weight of the patient fell from 202 lbs to 172 lbs in three weeks, losing 20 lbs in the first five days. This was the only occasion when such marked weight loss (edema loss) was not accompanied by the severest form of intoxication. During and following this period the patient felt unusually well and energetically strong.⁴² Gradually, however, because of the persistence of the circulatory inadequacy, the extremities became more and more edematous again and a second attempt on Oct 14, 1930, to produce free drainage resulted in a temporary loss of approximately 10 lbs in 10 days. On this second occasion drainage was scant and slow, the edema had become more firmly "fixed" in the intoxicated tissues and was retained with great tenacity; the tissue thirst^{3,8,9,10} had become more marked. Such surgical intervention in extensive edema of the extremities, of course, does not alter the hydration capacity of the tissue colloids so as to cause them to give up their bound water, nor does it in any way effect the etiologically significant malcirculation, except inasmuch as there is reduction of the mechanical obstruction due to the edema. Therefore the limitations of such mechanical drainage are notable; no physiologic diuretic effect is to be anticipated. However, the administration of the xanthin diuretics greatly increases the flow of serum from the vessels and it is felt that this is most

desirable. The one great advantage of such a route of elimination for the edema fluid is that the toxic debris and "edema toxins" are *not thrown into the circulation*; diuretic medication to the tissues liberates more of the fluid and thus the flow is enhanced.

Three important and often neglected clinical aspects of the problem of circulatory edema were repeatedly emphasized during this long struggle: edema fluid is poisonous; edema fluid caused profound intoxication when thrown rapidly into the circulation; concentration of these toxins by water deprivation increases the intoxication to a dangerous degree and for this reason the patient should be protected by an adequate fluid intake during diuresis and the subsidence of edema. Water itself is probably the safest diuretic if used with judgement and discretion. If edema is considered a protective mechanism, which we believe to be the case, the objective of therapy should not be limited to removal of the water alone but should consider of primary importance the removal, or the rendering innocuous, of the very toxic solutes in such fluid. Very rapid diuresis is dangerous, particularly in instances of edema of long duration. Dilution of the fluid by liberal water intake is desirable.

It is most important to realize that both clinically and pathologically there was no evidence of notable renal disease in the present case. Frequent analyses of the urine revealed a few casts, some epithelial debris, from 10 to 30 mg albumin per hundred cc (sulphosalicylic acid method), no sugar or pus. Anatomically at autopsy the renal tissue showed little or no parenchymatous

change both grossly and microscopically. The pathologic picture was that of long standing hypertensive arterial disease with arteriolar sclerosis,³ but no nephritis. Secondary injury, attributable to the hypertensive disease, was primarily cardiac. The unusual terminal accident of thrombosis of the femoral artery deserves a word of comment. What is most extraordinary is that arterial occlusion in an edematous extremity does not occur more often. So far as our search has gone we have been unable to find any other reported instances of such termination in congestive cardiac failure. The origin of the thrombosis was undoubtedly embolic, probably from the diseased aortic valve leaflets. It is but a very remote possibility that the surgical wounds about the ankle had anything to do with the arterial occlusion; they were clean and free from infection throughout the course and the occlusion occurred from above, not below. Occlusion of the femoral artery does not necessarily result in gangrene of the extremity as normally the collateral circulation suffices to maintain adequate nutrition, in the present instance, however, the

severe and prolonged edema markedly impeded the circulation and did not permit of sufficient oxygenation. Although the original prognosis had never been good, such an accident must inevitably mark the beginning of the end.

SUMMARY

In an unusually prolonged instance of congestive cardiac failure with extensive edema a number of pertinent clinical phenomena have been studied and reported. Clinical evaluation of a number of therapeutic agents is made. The behavior of the arterial tension during decompensation is discussed and the bases for the evaluation of the prognosis considered. Certain significant aspects of the clinical problem of edema in cardiac decompensation are emphasized. Another instance of aortic stenosis with calcification of the aortic cusps, recently described by Margolis and his associates⁷ and Christian³² as a distinct clinical entity, is recorded. Report is made of the unusual feature of termination by occlusion of the femoral artery in an edematous extremity.

REFERENCES

- ¹STIEGLITZ, E. J. Arterial hypertension, evaluation of prognosis, *Arch Int Med*, 1930, **XLVI**, 227-235.
- ²POST, W. E., and STIEGLITZ, E. J. Hypertension, clinical aspects of etiology and therapy, *Am Jr Med Sci*, 1926, **CLXI**, 648-654.
- ³STIEGLITZ, E. J. Arterial hypertension, 1930, Hoeber, New York.
- ⁴STIEGLITZ, E. J. Bismuth subnitrate in therapy of hypertension, *Jr Pharmacol and Exper Therap*, 1927, **XXXII**, 23-35.
- ⁵STIEGLITZ, E. J. Bismuth subnitrate in the treatment of arterial hypertension, *Jr Am Med Assoc*, 1930, **XLV**, 842-846.
- ⁶STIEGLITZ, E. J. Pharmacodynamics and value of bismuth subnitrate in hypertension, *Jr Pharmacol and Exper Therap*, 1928, **XXXIV**, 407-423.
- ⁷MARGOLIS, H. M., ZIEGLER, F. O., and BARNES, A. R. Calcific aortic valvular disease, *Am Heart Jr* 1931, **VI**, 349, 374.
- ⁸ALDRICH, C. A., and McCLELL, W. B. Time required for disappearance of intradermally injected water, *Jr*

- Am Med Assoc, 1923, lxxxi, 293-294
- ⁹BAKER, W. J Intradermal salt solution test in scarlet fever and diphtheria patients, Jr Am Med Assoc, 1924, lxxxiii, 1566-1567
- ¹⁰ALDRICH, C A, and MCCLURE, W B The intradermal salt solution test, Jr Am Med Assoc, 1924, lxxxii, 1425-1428
- ¹¹OLMSTEAD, E C Intradermal salt solution test in cardiac disease in children, Arch Int Med, 1925, xxxvii, 281-290
- ¹²BRAMS, W A The effect of digitalis on the electrocardiogram, Arch Int Med, 1929, xliii, 676-683
- ¹³EGGLESTON, C Influence of large doses of digitalis and digitoxin on the blood pressures in man, Jr Am Med Assoc, 1917, lxi, 951-955
- ¹⁴HATCHER, R A, and EGGLESTON, C Observations on the keeping properties of digitalis and some of its preparations, Am Jr Pharm, 1913, lxxxv, 203-214.
- ¹⁵SCHOLZ, W Die Behandlung der Herzschwache, Wien klin Wchnschr, 1928, xli, 1283
- ¹⁶EGGLESTON, C Digitalis dosage, Arch Int Med, 1915, xvi, 1-32
- ¹⁷LEVY, R L, and MACKIE, T T Drug treatment of heart disease, Jr Am Med Assoc, 1927, lxxvix, 432-436
- ¹⁸CLOUTTA, M The biochemical action of digitalis, Jr Am Med Assoc, 1929, xciii, 1462-1463
- ¹⁹HATCHER, R A, and EGGLESTON, C The emetic action of the digitalis bodies, Jr Pharmacol and Exper Therap, 1912 iv, 113-134
- ²⁰HATCHER, R A, and WEISS, S The seat of emetic action of the digitalis bodies, Arch Int Med, 1922, xliix, 690-704
- ²¹HATCHER, R A, and WEISS, S Reflex vomiting from heart, mechanism of vomiting induced by digitalis bodies, Jr Am Med Assoc, 1927, lxxvix, 429-432
- ²²LEWIS, J S Future of medicine, Clin Med and Surg, 1930, xxxvii, 516-520
- ²³METCALF, A H Studies on respiratory depressants, Jr Pharmacol and Exper Therap, 1930, xxxix, 212-5
- ²⁴LEYKO, E Action of some heart tonics, Jr Pharmacol and Exper Therap, 1930, xxxviii, 31-49
- ²⁵SCUUBEL, K, and GEHLEN, W Vergleichende Untersuchungen über atmungs-erregende Pharmaka am morphinvergifteten Kaninchen, Arch f exper Path u Pharmakol, 1928, cxxxiii, 295-316
- ²⁶EISNER, W Klinische Untersuchungen über den Einfluss des Coramins auf die Überleitungszeit des Herzens, Schweiz med Wchnschr, 1927, lvii, 574
- ²⁷SMITH, F M, GIBSON, R B, and ROSS, N G The diet in the treatment of cardiac failure, Jr Am Med Assoc, 1927, lxxxviii, 1943-1947
- ²⁸SMITH, H L Digitalis delirium with colored vision, report of one case, Jr Iowa Med Soc, 1931, xxi, 173-174
- ²⁹CORNWALL, E E Clinical significance of variations in the systolic and diastolic blood pressures and the pulse pressure, Internat Clin, 1915, xxv, s 1, 151-168
- ³⁰READ, J M Clinical interpretation of pulse pressure, Abridged in Cal and West Med, 1929, xxvii, 211-212
- ³¹READ, J M A clinical interpretation of pulse pressure, Am Heart Jr, 1927, ii, 541-547
- ³²CHRISTIAN, H A Aortic stenosis with calcification of the cusps, Jr Am Med Assoc, 1931, xcvi, 158-161
- ³³KEELER, C S, and RESNICK, W H Angina pectoris, syndrome caused by the anoxemia of myocardium, Arch Int Med, 1928, xli, 764-807
- ³⁴LOEB, J Proteins and the theory of colloidal behavior, 1922, McGraw-Hill, New York
- ³⁵FISCHER, M Edema and nephritis, 1915, John Wiley & Sons, New York
- ³⁶LOEB, L Edema, 1923, Williams & Wilkins, Baltimore
- ³⁷ANDRUE, E Experimental uremia, Arch Int Med, 1927, xl, 548-570
- ³⁸MCELENEY, J B Diseases of the kidney, Tice's Practise of Medicine, 1921, W F Prior Company, Inc, Hagerstown, vi, 581
- ³⁹KEITH, N M; WILLIAMS, M, and BA-

NICK, E G Action and excretion of nitrates, Arch Int Med, 1930, xlv, 797-832

⁴⁰STIEGLITZ, E J Alkalis and renal injury, Arch Int Med, 1928, xli, 10-17

⁴¹EPSTEIN, A A Quoted in Bannick, E G, and Keith, N M The treatment of nephritis and nephrosis with edema, Jr Am Med Assoc, 1928, xci, 1944-1952

⁴²BLAND E F, and WHITE, P D The use

of mechanical measures in the treatment of obstinate edema, Jr Am Med Assoc, 1930, xcv, 1489-1493

⁴³LIEBERMAN, A L Comparative studies on calcium gluconate and other calcium salts, Jr Am Med Assoc, 1931, xcvi, 15-16

⁴⁴BARACH, A L Therapeutic use of oxygen in heart disease, ANN INT MED, 1931, i, 428-440

Two Ways of Dealing with Unqualified Medical Sectarians

“THERE are two ways of dealing with the problem constituted by the existence of unqualified medical sectarians. One is the non-legal, and involves striking at the cultists by removing the causes which lead people to go to them. The second involves the legal suppression of the sectarians. The first approach, being the more fundamental, is in the long run the simpler and more effective. The major factors responsible for the growth of cults are credulity, ignorance and superstition on the part of the public. It is obvious that if the cults are to be eradicated, these failings must be remedied and people must learn more about the make-up and functioning of the human body. Furthermore, it is only as people gain an intelligent understanding of the human body that they can be led to understand the necessity for legal suppression of unqualified healing practitioners. To the extent that certain deficiencies in medical practice have contributed to the rise of present-day sects, the removal of those deficiencies will aid in the eradication of the sects.

“The second way of eliminating unqualified sectarians is through laws regulating the healing art. At the present time in the United States the legislative regulation of the healing art—regulation designed to protect the public from unqualified practitioners—is not accomplishing its acknowledged purpose. All it does is to maintain high standards for one group of practitioners. Quite illogically, it also sanctions the existence, on a lower plane of qualifications, of many thousands of poorly trained practitioners. Manifestly if the public is to be adequately protected, there must be a single minimum standard of qualifications for all healing practitioners.”

From *The Healing Cults—A Study of Sectarian Medical Practice Its Extent, Causes and Control* By LOUIS S REED, Ph D. The Committee on the Costs of Medical Care, 910 Seventeenth Street, N W, Washington, D C (Abstract of Publication No 16)

Generalized Myositis Fibrosa

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LOCALIZED disease of the muscular system of an acute or subacute nature, commonly designated muscular rheumatism, fibrositis, myositis, or myalgia, is of very common occurrence. Pemberton¹ has remarked that it is probably one of the most widespread and frequently occurring conditions to which human beings are subject, excepting mild infections of the upper respiratory tract. Quite in contrast to the above statement is the fact that inflammatory muscular diseases of a generalized nature, either acute, subacute, or chronic, are exceedingly rare. In the acute and subacute group four types are recognized: primary suppurative myositis which is only occasionally generalized, myositis, a result of *Trichinella spiralis* infestation, dermatomyositis, and polymyositis hemorrhagica which is probably a form of the latter condition. In the chronic group there are three types: the chronic form of dermatomyositis; myositis ossificans progressiva; and primary myositis fibrosa. The latter condition, primary

myositis fibrosa, is presumably the rarest of all types, there being only four typical cases reported in the literature, with perhaps as many doubtful or atypical ones.

RÉSUMÉ OF THE LITERATURE

Janicke² in 1895 reported the first typical, authentic case of generalized myositis fibrosa. Prior to this time Gies³ (1879) and Kreiss⁴ (1886) each described a case of myositis fibrosa which, however, can hardly be regarded as typical since the extent of the involvement of the muscles was small, the lower limbs only being affected, but particularly because there was also involvement of the overlying skin. Gowers⁵ (1899) in a lecture on polymyositis described an unusual case which has been designated as a case of myositis fibrosa in a recent review of the literature.⁶ In this case the intense pain at the onset of the illness, the early appearance of foot drop, and the loss of deep reflexes leads us to believe that the condition was perhaps a peripheral neuritis of widespread distribution with secondary atrophic changes in the muscles. Moreover, histological evidence to support the diagnosis of myositis fibrosa is lacking. The case of Batten⁷ (1904) was the first to be accompanied by a

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detailed pathological study. In 1923 Burton, Cowan, and Miller⁶ reviewed the literature and contributed an additional case. Hoover⁸ (1924) has briefly described a case which appears to be quite typical; however, it was not proved by histological examination of tissue. The same author reported a case of dermatomyositis (case 3) which is somewhat atypical for that disease in that the characteristic skin changes were not present and which, to the present writers, seems to resemble myositis fibrosa. Rosenstirn⁹ in his extensive review of the published cases of myositis ossificans progressiva found two cases which he thought had been erroneously diagnosed and which had extensive fibrous changes in the muscles rather than ossification. The first of these (Lexer,¹⁰ 1895) was characterized by a generalized distribution throughout the muscular system of fibrous nodules containing calcareous material. The second case is that reported by Krause and Trappe¹¹ (1907), and was thought by Rosenstirn to be a case of myositis fibrosa. In this case, the multiple nodules, many of which had undergone softening, and the extensive changes present in the skin would cast considerable doubt as to the validity of Rosenstirn's correction. Perhaps the most that can be said of both cases is that if they belong to this group they are exceedingly atypical.

ETIOLOGY

Little if anything is known concerning the etiology of this rare disease. It seems rather likely that it is related pathogenetically to the localized myositides in that the histological picture of the muscle tissue in general-

ized myositis fibrosa does not differ greatly from that in the later stages of fibrositis. If so, the disease may be added to that already very large group designated as the rheumatoid or arthritic syndrome. Batten⁷ suggested the possibility of this condition being allied to myositis ossificans progressiva largely because his case exhibited microdactylia of the large toes. Several facts concerning the two diseases renders this relationship not impossible. Ossification of muscle tissue in nearly all cases is preceded by a myositis. According to Rosenstirn,⁹ the primary pathological change in myositis ossificans is capillary hemorrhage, and Llewellyn and Jones¹² have shown that the early change in fibrositis is a dilation of the small blood vessels and capillaries, with not infrequently minute hemorrhages.

CASE REPORT

O. E., a negro boy, 14 years of age, a student by occupation, entered the John Sealy Hospital, January 3, 1929, complaining of stiffness of the entire body and pain in the chest.

Family History. Mother and father living and well, age 51 and 57, respectively. Five brothers and six sisters all living and well, the oldest being 33, the youngest 10 years of age. Negative history for syphilis, tuberculosis, and cancer.

Past History. Born at full term, normal delivery, the eighth child. He began walking at the age of 2. He was somewhat slow in talking and always stuttered badly. At the age of 7 he started to school and seemed to make normal progress, attaining the fifth grade at the onset of his illness. During childhood he was unusually healthy and the only disease which he had had was measles at the age of 9, from which he made an uneventful recovery. At the age of 10 he helped on the farm picking and planting cotton. He was regarded by his family as being a perfectly normal child except for

the stuttering, until the beginning of the present illness

Present Illness About one year prior to entry into the hospital he noticed a dull aching pain in the upper part of the chest. This symptom was present more or less continuously and was not intensified by respiration. He consulted a physician who gave him some medicine which caused the pain to disappear. At about the same time his mother noticed that he was not as "pert" as usual and that he seemed to move rather slowly and deliberately. However, he continued to go to school and to do odd jobs around the house. A few weeks later he noticed a peculiar stiffness in his hands which made it difficult for him to perform the finer movements without clumsiness. This stiffness slowly but progressively became worse. Four or five weeks after the recognition of the stiffness of the hands he noticed a similar state of affairs beginning in his legs which seemed to largely involve the knees and which interfered to some extent with walking. In September, seven months after the onset of his illness, he started to school as usual, but was unable to play with the other children as he had previously done because of clumsiness in walking and running. While doing calisthenics he noticed that he was not able to bend over as far as the other children and that his back seemed to be stiff and rigid. His appetite had remained good throughout his illness and as far as he could tell he had lost no weight. There was no constipation, nocturia, or polyuria. At no time during his illness had there been any fever or pain in his muscles or joints.

Physical Examination The general appearance was that of a dull, apathetic negro boy of about 15 years of age. He stuttered badly when he attempted to speak. Height, 5 feet and 9 inches, weight 117 pounds, calculated ideal weight, 140 pounds.

The face was non-expressive. No cervical adenopathy was present. The skin immediately surrounding the mouth was lighter in color than that of the face but no indentation was present. The conjunctivae and sclerae were pale. The lips were pale. The teeth were in good con-

dition. The tonsils were present, moderate in size and innocent in appearance.

The chest was of the asthenic type. Some deepening of the supra- and infra-clavicular fossae was noted. There was very little movement of the chest wall during respiration, breathing being entirely abdominal in character. Palpation and percussion resulted in negative findings. On auscultation the breath sounds were puerile, no râles were heard and the transmission of the spoken voice was normal throughout.

The cardiac impulse was diffuse in the third, fourth and fifth interspaces to the left of the sternum. No enlargement was made out by percussion. The heart sounds were loud and distinct. No murmurs were heard. The pulmonic second sound was markedly accentuated. The pulse rate was 88 and regular, the blood pressure, 116 mm Hg systolic, and 70 mm Hg diastolic. There was no evidence of arteriosclerosis in the peripheral vessels.

The abdomen was scaphoid. The liver and spleen were not palpable and there were no masses or areas of tenderness. Rectal examination was negative. The genitals were normally developed. Both testicles were present in the scrotum. The prostate was normal in size, shape, and consistency.

The skin over the entire body was apparently normal except over the wrists and hands, where it was shiny in appearance and seemed somewhat thinner than normal. However, it was pliable and not bound down to the underlying tissues. The hair was normally distributed over the body.

Practically all the muscles of the body, but some more than others, seemed to be indurated. To the palpating hand they imparted the sensation of being firmer and stiffer than normal, and not unlike a sand-bag. The muscle volume was fairly well preserved, with the exception of the deltoid and pectoral muscles which showed considerable atrophy. None of the muscles were painful either on palpation or movement. They seemed to have lost much of their normal elasticity with resulting limitation of movement. All movements of the face and lips were well performed. The masticatory muscles were involved to such an extent that when the mouth was opened a

widely as possible the distance between the incisor teeth was only 3 cm. The sterno-mastoid muscles were only slightly involved. The arms could be abducted only to an angle of about 60° with the chest wall and at that point further abduction was prevented by tightening of the tendons of the pectoral and latissimus dorsi muscles (figure 1a). Extension of the elbows was possible only to an angle of about 160° because of shortening of the biceps muscle (figure 1b). Flexion of the elbows was not interfered with. Passive movements of the wrists were easily performed within a certain range but were abruptly checked by a tightening of the flexor and extensor tendons. The fingers were held in a semiflexed position and any attempt to extend them fully was thwarted almost immediately by tightening of the flexor tendons. The muscles of the trunk and lower extremities were uniformly involved. The knees could be flexed only to an angle of approximately 100° due to shortening of the quadriceps femoris muscle (figure 1c). The strength of all involved muscles was definitely impaired. There was a very feeble grip of either hand.

The gait was somewhat spastic. All the cranial nerves were normal. Fundus examination was negative. All deep and superficial reflexes were present and equal. There was no disturbance of sensation anywhere in the body nor was there any paralysis.

Laboratory Examinations. The urine was entirely negative. There was a slight secondary anemia present: hemoglobin, 75 per cent (Sahli), red blood cells, 4,050,000 per cu mm, white blood cells, 12,000 per cu mm, with essentially a normal differential count. The blood and spinal fluid Wassermann tests were negative. Blood chemistry: total non-protein nitrogen, 30 mg, urea nitrogen, 11 mg, uric acid, 57 mg, creatinine, 13 mg, and sugar (fasting) 91 mg, per 100 cc of blood. Spinal fluid examination was entirely negative. The basal metabolic rate was plus 14. The phenolsulphonphthalein excretion was 55 per cent in two hours. An electrocardiogram showed sinus rhythm with low voltage in all leads with slurring of the Q-R-S complexes. All T waves were upright. X-ray examination

of the teeth, wrists, joints of the fingers, elbows, sella turcica, and skull were entirely negative.

Course in the Hospital. On admission the patient was afebrile but a week later he began to show a slight afternoon rise in temperature, 99° to 99.6° F. The pyrexia continued and gradually increased in degree. Two weeks later he complained of attacks of dyspnea which were especially troublesome at night and which were often accompanied by a dull aching pain over the precordium. He began to lose weight, 2 to 3 pounds a week. On several examinations of the chest it was now noted that moist râles were present in both apices. After a stay in the hospital of about two months the elevation in temperature became a more or less constant feature, usually reaching 101° F, in the afternoon. A tachycardia was constantly present. The physical signs in the chest became more pronounced and an X-ray study revealed evidence of an infiltrative lesion in both apices, which was thought to be tuberculous in nature. There was no cough or expectoration and as a result sputum could not be obtained for examination. Weakness became a prominent symptom and eventually he was confined to bed. Dyspnea was evoked on the slightest exertion. His condition gradually became worse and death occurred three months after admission.

Autopsy. Necropsy was performed five hours after death. Rigor mortis was present. On incising the pectoral and abdominal muscles they appeared to be lighter in color than normal and to cut with increasing resistance. The heart weighed 280 gm. The valves were normal with the exception of the pulmonic leaflets which showed slight fenestration. The myocardium was abnormally light in color. The left lung contained an area of consolidation in the lower portion of the upper lobe and the overlying pleura was dotted with greenish white nodules measuring 1 to 2 mm in diameter. Section of this region of the lung revealed multiple areas of caseation. The right lung was apparently normal. The hilar nodes were enlarged and on section showed multiple greenish areas. The mediastinal nodes were likewise enlarged and on section were greenish.

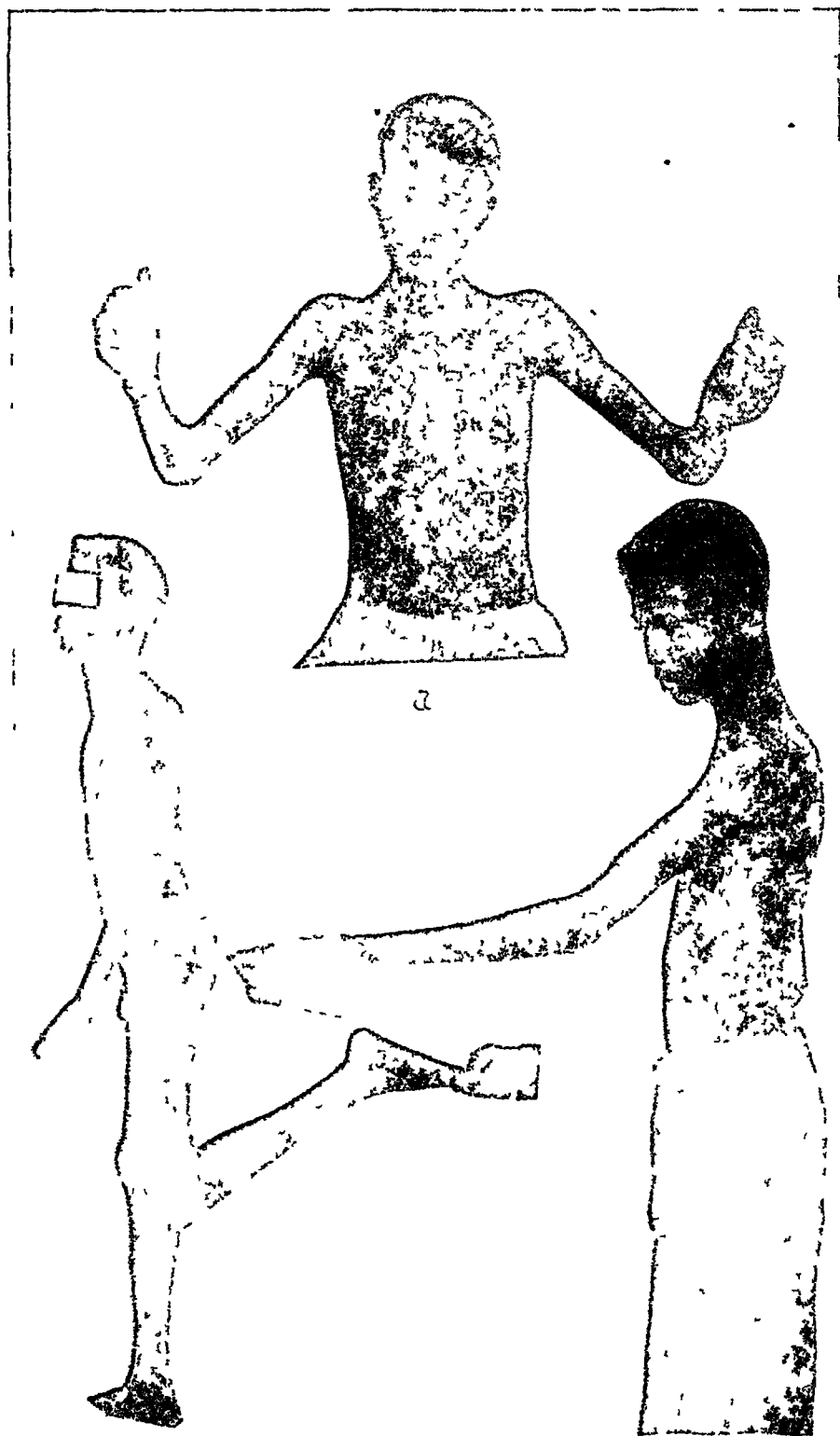


Fig. 1. Illustrations of the impairment of muscle function, (a) showing maximum extension of elbows, and (b) maximum flexion of elbows.

ish in color with their central portions semi-fluid in consistency and of a turbid, greenish color. The liver and spleen were larger than normal, their respective weights being 1860 and 230 gm. There was one small area of caseous necrosis in the spleen. No abnormal changes were noted in the kidneys, stomach, adrenals, pancreas, intestines, testicles, and urinary bladder. Permission was not granted for examination of the brain and spinal cord.

Microscopic Findings The consolidated area in the left lung and the lymph nodes of the hilus and mediastinum showed evidence of an acute tuberculous process in the form of miliary and conglomerate tubercles along with liquefaction necrosis, especially in the nodes. The myocardium was abnormal in that there was a slight increase in the size of the fibers with a more granular cytoplasm. There was also a slight increase in fibrous tissue and in this were found a few scattered mononuclear, inflammatory cells. Parenchymatous degen-

eration and hyperemia were noted in the kidneys.

The histological examination of the *voluntary muscles* resulted in extremely interesting findings. Prior to death, specimens were obtained from the soleus and quadriceps femoris muscles. At autopsy tissue was procured from the following muscles: rectus abdominis, psoas, iliacus, pectorals, sartorius, diaphragm, intercostals, and deltoid. On gross examination the muscles were distinctly lighter in color and had a somewhat greyish tint. On palpation they were firmer than normal and on section cut with increased resistance.

Microscopically, degenerative, inflammatory, and fibrous tissue changes were found (figures 2 and 3). The three types of change were present in



FIG. 2 Longitudinal section of the rectus abdominis muscle. Note the small size of the individual fibers, their complete destruction in some areas, and the infiltration with inflammatory cells.

all muscles, varying, however, in degree. In both longitudinal and cross sections the individual muscle fibers exhibited great variation in size, some of them appearing larger than normal, whereas others were reduced to as much as a fifth their normal diameter. In many fibers, all striations had disappeared while in others the longitudinal striations only were present with loss of the transverse ones, and *vice versa*. Hyaline degeneration and hy-

dropic infiltration were commonly noted. Scattered throughout the muscle tissue were varying numbers of inflammatory cells and in certain areas they formed definite collections. In such areas the muscle tissue had undergone more or less complete degeneration. By far the larger number of these cells were of the lymphocytic group. A small number of plasma cells were present along with large endothelial cells and fibroblasts. Only



Fig. 1. Cross section of the sartorius muscle. Note the hyaline degeneration and the collection of inflammatory cells.

an occasional polymorphonuclear cell was noted. Variable amounts of new fibrous tissue were found in different muscles, and constituted approximately 10 per cent of the muscle volume. This change was most marked in the iliacus, quadriceps femoris, rectus abdominis, and deltoid muscles. None of the fibrous tissue had reached the adult type. Microscopic study of the peripheral nerves revealed no departure from the normal. A more detailed description of the histopathology will be presented in a future communication.

THE CLINICAL PICTURE

A summary of the clinical findings in the reported cases is outlined in table 1. Age and sex apparently play no part as predisposing factors in the causation of this disease. The youngest case occurred in an infant of 9 months, whereas the oldest was in a man of 48 years. Males and females appear to be equally affected. Our case is the only one reported occurring in the negro race.

The onset of the disease is insidious but once begun seems to progress fairly rapidly, the process requiring only a few months to cause definite impairment of muscle function. Batten's⁷ case required 5 years to reach an advanced stage, whereas Hoover's⁸ case was rendered an invalid in two years. In the case here reported the process developed more rapidly, producing invalidism in about 9 months. Previous diseases or infections were in some instances incriminated as factors in the causation of the muscular condition. The case of Burton, Cowan and Miller⁹ had had a pyelitis prior to the onset of symptoms and also frequent

sore throats. In their case it is also interesting to note that there were exacerbations with each pregnancy. The questionable case reported by Gies¹ had a carbuncle on the back a year previously. Our case apparently had a quiescent pulmonary tuberculosis at the time of admission.

The presenting symptom in practically all of the cases was a feeling of stiffness in the extremities associated with inability to perform voluntary movements without clumsiness. This symptom became progressively worse as the disease advanced, ending eventually in marked limitation or complete loss of contractility of the involved muscles. Usually the first muscles to be affected are those of the extremities, most often the lower. The condition then gradually spreads to eventually involve nearly every muscle in the body. The muscles of the face and lips have apparently escaped in all cases that have been thus far described.

Considering the pathological changes present in the muscle tissue, one would expect pain to be a prominent and conspicuous symptom. On the contrary, it was entirely absent in the majority of the reported cases, and in those in which it was present, it occurred early in the disease and was a minor complaint of short duration. Janicke's² case had slight pain early in the course of the disease. In Hoover's⁸ case and that reported by Gies¹ the muscles were said to be sensitive to pressure. Weakness and loss of weight were the outstanding constitutional symptoms. Fever was not mentioned as occurring in any of the cases.

The characteristic feel of the muscles on palpation is the outstanding

TABLE I
A Brief Summary of the Clinical Findings in the Reported Cases of Generalized
Myositis Fibrosa

Case No.	Sex	Race	Presenting Symptom	Flap	Pain	Extent of Involvement	Duration	Skin Lesions	Outcome	Remarks
1	F	W	Swelling of the sternomastoid muscle and stiffness of the neck	None	Yes, early Not severe	Generalized, most marked in the neck, shoulder girdle, and arms	1 month	None	Improved some under treatment Progressive, not followed	Under observation 4 months
2	M	W	Stiffness of the arms and legs	None	None	Generalized, began in legs and abdomen	5 years	None	Death	Marked contractures
3	F	W	Drawing up of the legs	None	None in the muscles, the some in shoulder	Generalized except muscles of face Considerable atrophy	2 years	Skin of hands involved later	Living at present	Pyelitis and frequent sore throats Worse during pregnancy
4	F	W		None	Muscles were sensitive to pressure	Generalized with marked atrophy	2 years	None	Death	Not proven microscopically
5	M	W	Pain in the rt leg, later painful swelling of the thigh	None	Pain on palpation	Muscles of rt thigh, later the calf muscles of same leg	Several months	Overlying skin like leather, adherent to muscles	Improved under treatment	Carbuncle a year before onset of illness
6	F	W	Fatigue, pain in the back, and stiffness of the legs	None	Early but none later in the course of disease	Practically every muscle in body Marked atrophy	1 year?	Rash over arms and hands early	Not followed	Not proven microscopically Loss of reflexes
7	M	W	Stiffness of the legs	None	None	Calf muscles of both legs	3 years	Skin over muscles hard and indurated	Improved under treatment Not followed	Arthritis of both knees during illness Similar attack before
8	M	B	Stiffness of the legs	None	None	Generalized except small muscles of face	1 year	None	Death	Pulmonary tuberculosis

diagnostic point. The muscles feel distinctly harder than normal and seem to be increased in consistency. To the palpating hand they impart the sensation of being edematous without any extension of the process to the subcutaneous tissues, they may be described as doughy or boggy. In the early stages of the disease the muscle volume is well preserved, in advanced stages there is a marked decrease in size and on palpation the muscles feel hard and boardlike. With the decrease in size of the muscles, resulting from contraction of scar tissue, there is an associated shortening which produces marked limitation of movement, a condition which eventually renders the patient completely helpless.

DIAGNOSIS

Although positive diagnosis is possible only after microscopic examination of the muscles, their characteristic feel on palpation, the impairment of their function, the absence of pain, the lack of constitutional symptoms, and the chronic progressive nature of the condition constitute a clinical picture which can be confused with few other diseases. The absence of skin lesions readily differentiates myositis fibrosa from the chronic form of dermatomyositis. The primary progressive myopathies or muscular dystrophies offer little difficulty in the differential diagnosis. The familial manifestations, the tendency to a symmetrical involvement of muscle groups, and the marked atrophic, or in some instances the pseudohypertrophic, changes in the muscles are the outstanding points to be remembered. In the myopathies weakness of the involved muscles is

the outstanding symptom, whereas in generalized myositis fibrosa stiffness of the muscles is the predominant functional derangement.

CREATINE METABOLISM

A detailed study of the creatine metabolism having been reported in an earlier publication,¹³ only a brief summary of the essential findings will be attempted in this connection. Derangement of the creatine-creatinine metabolism, particularly as regards the abnormal excretion of creatine in the urine, is a well-known manifestation of muscle disease. In the present case the creatinuria was particularly marked, more than 40 per cent of the so-called "total creatine"* being excreted as creatine, even on a meat-free diet. For the critical evaluation of this result two complicating factors should be borne in mind, the age of the patient and the co-existence of tuberculosis. As to the influence of age, there is inadequate information concerning the creatine metabolism in early adolescence, but such data as are available indicate that at the age of 14 and 15, creatinuria is either absent or of relatively small quantitative importance. Of perhaps greater significance is the influence of pulmonary tuberculosis. On the one hand, there are the careful observations of McClure¹⁴ which demonstrate that creatinuria is not characteristic of this disease and on the other hand there is the work of Thompson¹⁵ which emphasizes that creatinuria is associated with pulmonary tuberculosis. It is perhaps

*This refers to the total excretion of creatine and creatinine expressed as a percentage of creatinine.

judicious, therefore, to admit, for the present, the possibility that the age of the patient and the co-existing tuberculosis were contributory factors, but at the same time, it is quite obvious that the high grade of creatinuria was due primarily to the disease of the muscular system

Since the creatine-creatinine metabolism reflects the endogenous metabolism, moderate variations in protein intake exert little, if any, effect in the normal individual, the creatinine excretion being maintained at a practically constant level. In contrast to this is the pronounced effect which the addition of meat to the diet produced in the case under consideration. With an increase in protein metabolism of approximately 70 per cent (from 10 gm of urinary nitrogen in 24 hours to 17.07 gm), the "total creatinine" was raised from 1.28 gm to 2.25 gm, an increase of 1.27 gm, of which 0.99 gm (78 per cent) was in the form of extra creatine.

Normal human voluntary muscle contains approximately 400 to 500 mg of creatine per 100 gm. Apparently it is capable of storing creatine above this level, as shown experimentally by Chanutrin¹⁶ and as is evidenced by the fact that if creatine is fed a considerable portion is retained. The storage of creatine proceeds until a point is reached when more and more of the ingested creatine is excreted in the urine. Presumably a level of saturation exists and after it is attained practically all of the ingested creatine, even in the normal individual, is promptly eliminated in the urine. It has been observed by one of us (M. B.) in unpublished experiments on

himself, that when 10 gm of creatine hydrate are ingested daily, the amount of creatine eliminated, though small at first, increases daily, but just as soon as the feedings are discontinued, creatinuria promptly disappears. The creatinine level of excretion, however, remains elevated for a considerable after-period, the extra creatinine owing its origin to the metabolism of a part of the extra creatine stored in the muscle (see also Benedict,¹⁷ Rose *et al*¹⁸). It is well known that this capacity for the storage of creatine is diminished in various muscle diseases, and therefore it was not surprising to find that this was true also in myositis fibrosa. Nevertheless, it was remarkable that there was almost complete inability to store the creatine for more than very short periods. On the administration of 1 gm of creatine hydrate (equivalent to 0.758 gm of creatine, in terms of creatinine), all was recovered within 24 hours, 92.1 per cent as creatine and the remainder as creatinine. On feeding 2 gm of creatine hydrate, 91 per cent was recovered within 48 hours, and in a subsequent experiment, 96.5 per cent. When 5 gm were fed, 91.73 per cent was recovered within 3 days. The obvious explanation is that the muscles possessed low saturation levels, so low in fact that even the creatine arising from the endogenous metabolism could not be retained sufficiently long to permit its normal metabolism to creatinine.

Analysis of various muscles, most of which were obtained soon after death, showed that their creatine content was abnormally low in all instances and as has been stated else-

where,¹³ a definite relationship was demonstrable between the creatine content and the degree of inflammation. Thus, the soleus which showed least inflammation contained the largest amount of creatine (324 mg per 100 gm), whereas the iliacus which showed the greatest degree of inflammation, contained, next to the diaphragm and myocardium, the least amount of creatine (160 mg). It is worth noting that the diaphragm and heart muscle likewise showed definite pathological changes (degeneration, inflammation, fibrosis). The former contained 159 mg of creatine per 100 gm of tissue, as compared with normal values of 357 to 364 mg obtained by one of us¹⁰ with the same method of analysis (Ochoa and Valdecasas²⁰). The myocardium also contained 159 mg of creatine per 100 gm. Analysis of heart muscle in two cases of sudden accidental death yielded values of 265 and 285 mg, respectively.

The inescapable conclusion is that in myositis fibrosa a definite relation exists between the degree of inflammation and the amount of creatine which the muscle contains and which it is capable of storing. For purposes of comparison, the composition of dis-

eased and normal muscle is summarized in Table II.

These results have a double significance. In the first place it is quite obvious that the creatine content of muscle in myositis fibrosa is much lower than normal, in the second place these closely approach the saturation level, whereas the data given for normal muscle are perhaps 10 to 30 per cent below the saturation level.

The uric acid content of the blood was relatively high, averaging 5.5 mg per 100 cc in a series of six analyses of the blood taken at different times during the course of the disease. In part this may be attributed to the co-existing tuberculosis and in part to the somewhat exaggerated nuclear metabolism accompanying the destructive changes in the muscle.

From the standpoint of diagnosis, the marked creatinuria and the extremely low tolerance for exogenous creatine are considered to be valuable criteria, as is also the low creatine content of the muscle.

PROGNOSIS AND TREATMENT

A consideration of the small number of reported cases justifies the conclusion that the outlook is not hopeful.

TABLE II
The Creatine Content of Muscle Normally and in Myositis Fibrosa
Muscle creatine in mg per 100 gm of fresh tissue*

MUSCLE	NUMBER OF SUBJECTS	NORMAL	MYOSITIS FIBROSA
Diaphragm	(3)	357-364-364	159
Myocardium	(2)	268-285	159
Deltoid	(2)	421-470	197
Sartorius	(1)	442	220
Intercostals	(2)	442-368	172
Psoas	(3)	470-483-470	220
Soleus	(1)	422	324

*Analysis by the method of Ochoa and Valdecasas.

The disease is progressive in nature. Its duration is variable. Batten's⁷ case lived 5 years. The one reported by Burton, Cowan, and Miller^{6,21} is living at the present time. Hoover's⁸ case lived only two years. In the remainder of the cases the duration of life was not mentioned. In the later stages of the disease the patient's general health undergoes marked deterioration and death from some intercurrent infection is probable.

Little can be said as regards therapy. Drugs are of no value. Massage has been very beneficial in one of the reported cases.⁶ Careful search for foci of infection should be made and when found such should be eradicated if possible as this measure might have some influence on the course of the disease. Massage, gymnastic exercises, and electrotherapy theoretically should be beneficial.

REFERENCES

- ¹PLIMBERTON, R. Diseases of muscles, Blumer's Bedside Diagnosis, 1929, W B Saunders Co, Philadelphia, 1, 624
- ²JANICKF. Myositis interstitialis, Deutsch med Wchnschr, 1895, xxi, 117
- ³GIFS, T. Über Myositis chronica, Deutsch Ztschr f Chir, 1878, xv, 161-168
- ⁴KREISS. Ein Fall von primärer schwerer Myositis der Wadenmuskeln, Berl klin Wchnschr, 1886, xxiii, 877-881
- ⁵GOWERS, W R. A lecture on polymyositis, Brit. Med Jr, 1899, 1, 65
- ⁶BURTON, J A G, COWAN, J, and MILLER, H. Generalized myositis fibrosa, with the report of a case, Quart Jr Med, 1923-24, xii, 103-111
- ⁷BATTEN, F R. Case of myositis fibrosa, with pathological examination, Trans Clin Soc, Lond, 1904, xxxvii, 12-22
- ⁸HOOPER, C F. Diseases of Muscles, Tice's Practice of Medicine, 1924, W F Prior Co, Hagerstown, Maryland, vi, 543
- ⁹ROSENSTERN, J. A contribution to the study of myositis ossificans progressiva, Ann Surg, 1918, lxviii, 485-520
- ¹⁰ROSENSTERN, J.
- ¹¹KRAUSE, P, and TEALPE, M. Ein Beitrag zur Kenntnis der Myositis ossificans progressiva. Fortschritte d. Geb d. Röntgenstrahlen, 1907, vi, 229-260
- ¹²ROSENSTERN, J, and JONES, A B. Fibrous degeneration of muscle, New York, 1925, Putnam Co, New York
- ¹³ROSENSTERN, J, SCHWAB, E H, and BURTON, J A G. Generalized myositis fibrosa, Quart Jr Med, 1931, xxxiv, 369-370
- ¹⁴McCLURE, C W. The excretion of creatine, creatinine and uric acid in acute febrile conditions, Arch Int Med, 1918, xii, 719-749
- ¹⁵THOMPSON, J T. Creatinuria in tuberculosis, Jr Lab and Clin Med, 1930, xvi, 5-11
- ¹⁶CHANUTIN, A, and SILVERTE, H. The influence of fasting and creatine feeding upon the creatine content of the tissues and blood of the white rat, Jr Biol Chem, 1928, lxxx, 589-608
- ¹⁷CHANUTIN, A. Studies on the creatine and nitrogen content of the whole rat after the feeding of a variety of diets and after nephrectomy, Jr Biol Chem, 1930, lxxxix, 765-774
- ¹⁸BRUNFELDT, S R, and OSTERNBERG, E. Studies in creatine and creatinine metabolism, Jr Biol Chem, 1923, lvi, 229-252
- ¹⁹ROSE, W C, ELLIS, R H, and HILMING, O C. The transformation of creatine into creatinine by the male and female human organism, Jr Biol Chem, 1928, lxxvii, 171-184
- ²⁰BODANSKY, M. Creatine in human muscle, Jr Biol Chem, 1931, xci, 147-149
- ²¹OGURA, S, and VALDECASAS, J G. A micro method for the estimation of total creatinine in muscle, Jr Biol Chem, 1929, lxxxi, 351-357
- ²²BURTON, J A G; COWAN, J M, and MILLER, H. Generalized myositis fibrosa, Quart Jr Med, 1931, xxxiv, 369-370

Roentgenologic Diagnosis of Early Pulmonary Tuberculosis

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THE value of roentgen rays in the early diagnosis of pulmonary tuberculosis has been a theme of controversy in the past, on the assumption that it was a rival of the clinical examination. At present it is commonly granted without question that the two methods are complementary, mutually helpful, mutually corrective, and almost indispensable to each other. Accordingly, the practitioner of either may point out its advantages without seeming to boast, or admit its limitations without seeming to make reluctant concession.

With respect to the technic of roentgenologic examination of the lungs, it will be sufficient to say that roentgenoscopic study is inadequate either to disclose or exclude the presence of small tuberculous lesions, and that roentgenography, which preferably should be stereoscopic and rapid, is essential for decisive results. At The Mayo Clinic it has been found advantageous to make the roentgenograms at

a distance of six feet, with high milliamperage and an exposure time of only a fraction of a second. By this means the blurring and obliterating effect of voluntary, respiratory or cardiac movement is precluded.

Obviously roentgen rays cannot reveal evidences of tuberculosis until demonstrable differences of density of the tissues have been produced by the infection. Rarely, cases with clinical manifestations suggestive of the disease give no roentgenologic signs. But the converse occurs far more often, and very many cases can be cited in which the affection was disclosed by roentgen examination when clinical symptoms and signs were vague and trivial, or absent altogether. Sampson and Brown¹ have said that in a surprisingly large number of cases definite changes characteristic of tuberculosis are seen in the film long before definitely abnormal physical signs can be detected. They have stated, further, that among 1367 consecutive cases at Trudeau Sanatorium, the physical signs in 32 per cent were either absent or so slight that the diagnosis was established entirely, or in large part, from study of the films. Webb² has said, succinctly, that roentgenologic examination is the chief method

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od available for detecting early pulmonary tuberculosis

EARLY TUBERCULOSIS OF ADULTS

Almost all cases of incipient tuberculosis of adults may be divided into two groups. In the first group, which comprises by far the greater number, the earliest significant manifestation is a relatively faint shadow in an upper lobe, more often that of the right lung (figures 1*a* and *b*). As seen stereoscopically, the dense region is more or less conical, on the single film it appears to be fan-shaped. Its base is at the periphery of the lung, and is often directed toward the axilla, its apex points toward the hilum. It lies obliquely below the clavicle, usually in the first interspace, occasionally in the second, and its long axis corresponds to an external twig of the ascending branch of the main bronchus. On close

inspection, the shadow is seen to be made up of a confused network of delicate lines enveloped in a filmy veil. Its appearance has been likened aptly to that of a web spun by caterpillars about an outer branch of a tree.

In the second group, the lesions are likewise situated in the outer parenchymatous portion of the subclavicular region but are more or less spherical in form (figure 2*a*). More often they are multiple, but they may be single. When multiple they are grouped, but in such variable degrees of proximity to each other that they may plainly be discrete or apparently confluent. Their size varies from a diameter of 1 or 2 mm to several centimeters, and multiple foci are likely to be diverse in size. Their shadows are faint, although denser at the center than at the periphery, the latter being especially hazy and indistinct.



FIGURE 1. *a*, Left upper lobe, showing a faint shadow; *b*, close-up of roentgenogram.

Common to both groups is an accentuation of the bronchovascular trunk leading from the affected region to the hilum. Occasionally the ribs on the affected side descend more steeply, and the intercostal spaces are narrowed, although these phenomena more often accompany advanced than early disease. Not infrequently the unaffected lung appears to be more brilliantly transradiant than normally. Roentgenoscopically, respiratory excursion of the diaphragm on the diseased side is likely to be restricted, and the apex is often less bright than its fellow. But restriction of diaphragmatic movement occurs in many diseases other than tuberculosis, and apical darkening not only has other pathologic causes but is often devoid of significance. Lesions in the apical field above the clavicle are rarely en-

countered early in tuberculosis, when they are present the disease almost invariably is well advanced and then its manifestations below the clavicle are more conspicuous.

In the differential diagnosis four prime characteristics of early tuberculosis are to be kept in mind: namely, its situation below the clavicle and in the outer parenchyma of an upper lobe, the roughly conical or spherical form of the lesions, the softness and lack of marginal definition of the shadows, and the accentuation of the tributary bronchovascular stem. Few of the simulants have all these characteristics. Among such simulants to be considered are bronchiectasis, malignant metastasis, the lateral border of an azygos lobe, shadows from extraneous causes, accentuation of bronchovascular markings without correspond-



FIG. 2a. Nodular type of lesions in right upper lobe, shadow is conical, comma and representing the outer border of an azygos lobe.

ing parenchymal shadows, localized simple pneumonitis, and small, healed, tuberculous lesions

Bronchiectasis in an upper lobe is usually depicted as a mottled, irregularly triangular shadow with its apex toward the hilum. However, bronchiectasis seldom affects upper bronchi, even in this event the lesion is essentially bronchial, and, although the corresponding parenchymal alveoli may be atelectatic, the more striking shadows are central rather than peripheral.

A malignant metastatic nodule in the infraclavicular region may imitate an early conglomerate tubercle. But metastatic nodules are most often numerous when discovered, and are likely to be widely scattered in several lobes. Further, a metastatic nodule is likely to be more regularly spherical, denser, and more sharply defined than a tuberculous nodule. An azygos lobe in the superior mesial portion of the right lung is not altogether rare (figure 2b). Its lateral border is represented by a curving shadow resembling an inverted and elongated comma. Since an azygos lobe is somewhat unusual, this shadow may be mistaken for an indication of disease, and its situation may suggest the thought of tuberculosis, but other essential features of tuberculosis are lacking. During the process of roentgenography, certain patients, especially women, are sometimes permitted to wear a cape, or other light clothing which may produce a faint shadow over the apical region. On inspection, however, the cause of the shadow should be apparent, but it is not infrequently the patient's chest is not properly exposed.

adults habitually arises from recrudescence of the primary infection acquired in childhood by retrograde extension from the hilar nodes into the lymphatic channels, especially the upper trunks, and thence into the parenchyma of the lung, has been responsible for many wrong diagnoses. This hypothesis was popularized by certain continental roentgenologists, and until a few years ago was widely accepted. Intensification of the hilar shadow and of the principal vascular markings, together with a so-called beaded or varicose appearance of the trunks, was deemed sufficient warrant for the diagnosis of "peribronchial tuberculosis." In the course of time, however, it was learned that frank tuberculosis almost never developed in cases in which such manifestations occurred, and that these appearances are often found in persons in robust health. Then the phrase, "peribronchial thickening" came into frequent use, but this expression is equivocal and so susceptible of erroneous interpretation that it is falling into disfavor. At all events, few roentgenologists will take responsibility for even a tentative diagnosis of tuberculosis unless the abnormal shadows extend to the peripheral portion of the lung, where shadows of the vessels are not normally visible.

Restricted, simple pneumonitis in an upper lobe, resulting from a cold or other ordinary infection, is a highly deceptive simulant of early tuberculosis. The morbid change may appear as a faintly shadowed conical segment, probably representing congestion chiefly, or as a small mottled patch depicting narrowly localized bronchopneumonia. In either instance the situation

and general character of the shadow, together with the intensification of the corresponding vascular marking, are identical with those of one or the other type of early tuberculous lesion, and the roentgenologist will be inclined consistently to make the latter diagnosis, at least provisionally. It is in such cases that the clinician can avert a wrong diagnosis by temporarily withholding final judgment, observing the course of the disease, and sending the patient for reexamination later. Fortunately, the acute, simple, pulmonary infections usually attack lower lobes, and invasion restricted to an upper lobe is rare, but it should be kept in mind when colds, pneumonia or influenza are prevalent.

ACTIVITY

Inability of the roentgenologist to distinguish with precision between ar-

rested and active lesions is an important source of error. The majority of healed lesions are dense and sharply delimited from the normal tissue (figure 3a), they are likely to be accompanied by calcified lymph nodes at the hilum or elsewhere, often the interlobar pleura, especially that of the right upper interlobar fissure, is visibly thickened. Conversely, most of the early active lesions cast thin shadows which merge indefinitely with those of the normal tissue, and they are seldom associated with calcified nodes or interlobar thickening (figures 1, *a* and *b* and 2*a*). But between the cases which are manifestly active and those which are plainly inactive, are many in which the degree of density and of marginal definition is hard to evaluate, and decision depends too largely on the personal equation of the examiner. Sometimes,

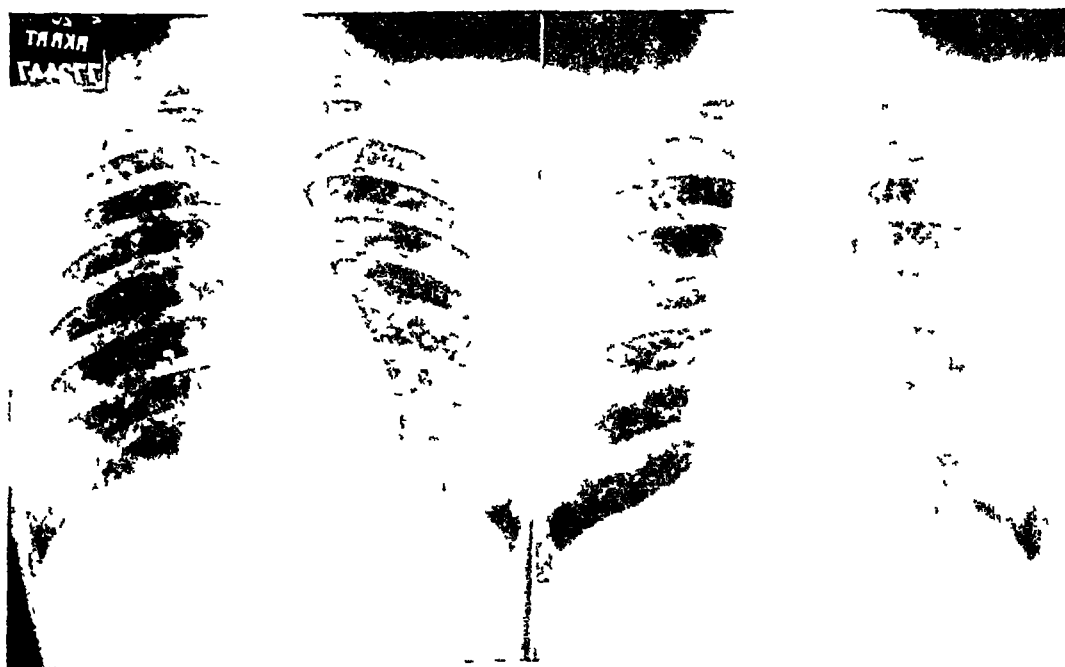


FIG 3a. Healed tuberculous lesions in the upper lobes. In the left upper lobe a tubercle in seventh interspace, posteriorly of left hilum. Calcified lymph nodes may be noted.

also, the roentgenologic indexes of activity or inactivity are not reliable; an apparent perifocal haziness may be the result of movement; lesions remote from the film appear less dense and less clearly defined than they would if near the film, density and marginal definition vary with the quality of the rays. For these reasons the roentgenologic opinion should always be subject to clinical review. As a single test of activity the roentgenologic examination is probably equal to any other; but no single test is a sufficient basis for such a momentous decision.

In very rare instances tuberculosis of adults is limited to a lower lobe or to the circumhilar region, and its manifestations are identical with those often observed in children. Although the pathologic changes are obvious at an early stage, the roentgenologist cannot logically attribute them to tuberculosis. In fact, when abnormal shadows are found only in a middle or lower lobe, the presumption is strong that they are not due to tuberculosis but to some other disease. As a rule, the appearance is suggestive of restricted, simple bronchopneumonia, and is so interpreted. The symptoms and physical signs are also so contradictory or confusing that usually the proper diagnosis is made only after a period of observation.

TUBERCULOSIS OF CHILDREN

Early tuberculosis of children has many points of difference from that of adults. It is commonly accepted that, before puberty is reached, virtually all children within the precincts of a tuberculosis have been infected with the bacillus of tuberculosis, and Ghon's

theory that the initial pulmonary lesion arises in the parenchyma is generally endorsed. But wherever the portal of entry may have been, the intrathoracic lymph nodes are by far the most common manifest site of reaction to this infection. Subsequently any of several results may follow: (1) healing or arrest, as occurs in the great majority of cases, (2) development of clinically important, primary, focal tuberculosis directly or indirectly from the parenchymatous or nodal focus, (3) development of miliary tuberculosis, and (4) development of an adult type of tuberculosis from new, secondary infection after subsidence of the primary infection.

Since primary tuberculous infection in children is the rule, roentgenologic confirmation of the fact, even if feasible, would be superfluous. A few roentgenologists have interested themselves in the Ghon focus. This is commonly small, situated in any lobe, whether upper or lower, and revealed as a variously shaped shadow in the parenchyma, but only after the lesion has passed its earlier stages (figure 3, *b*). Such a shadow is likely to be found in the roentgenogram of any child's chest, but identification of the shadow as that of a Ghon focus is necessarily uncertain. A roentgenologic diagnosis of tuberculous mediastinal lymphadenopathy is also insecure. In roentgenograms of children who have no clinical evidence of disease, the mediastinal shadow is usually wide, the lymph nodes about the hilum on both sides are frequently depicted, and the larger vascular markings seem to be accentuated. If the subject were an adult the picture would be abnormal, but since it is usual in

childhood it must be rated as normal. Often, especially in younger children, the adenopathy is more pronounced; the mediastinal shadow is vastly widened bilaterally, and its borders may be straight, convex, or polycyclic. However, identical manifestations may follow various infections of childhood, especially measles or whooping cough, and may persist for many weeks. In any case, therefore, the cause of the adenopathy is a problem to be solved by the clinician rather than the roentgenologist. Even when the primary infection in children has given rise to early parenchymal disease of actual or potential moment, difficulties in its roentgenologic recognition persist. The lesion may appear in any of the lobes, but it has a predilection for the circumhilar region or for the lower portion of the lobe invaded. Its shadow is of sufficient size and density to be obvious and may be somewhat fan-shaped, or irregular, or, if at the hilum, irregularly hemispherical. Wherever it may be, it inclines to a central, rather than a definitely peripheral situation. The mediastinal shadow is widened, perhaps lobulated, and the radicular markings are emphasized. On the whole, the picture is rather plainly that of localized pneumonitis, but whether simple or tuberculous can scarcely be determined positively from the roentgenologic appearance alone. If the examiner attempts to carry his interpretation farther he will be likely to consider bronchopneumonia, tuberculosis, and lobar pneumonia, the order of choice varying according to his most impressive experience and the more striking features of the case at hand. Always, if he is duly cautious, he will

make his diagnosis conditional on clinical confirmation and will suggest the various alternatives. The clinician also is often hampered by the indefinite or eccentric physical signs and the difficulty of obtaining satisfactory sputum tests so that extended observation may be required for final decision.

MILIARY TUBERCULOSIS

Inasmuch as diffuse hematogenous miliary tuberculosis often arises from a small hidden pulmonary or nodal focus or from one which is remote and unsuspected, it is perhaps entitled in such circumstances, to inclusion among early forms of the disease. In the absence of definite knowledge of an antecedent focus an independent clinical diagnosis is almost impossible, whereas roentgen rays usually will reveal the condition and often identify it positively. During the earliest stages of pulmonary invasion roentgen rays may fail to disclose any evidence of the disease, and death may occur, especially of infants before any changes can be demonstrated on the film. Notwithstanding such exceptions, roentgen rays in the majority of cases give a definite picture and one which is perhaps the most characteristic of any variety of tuberculosis. At first, mere veiling of the pulmonary markings may be seen, but shortly the tubercles also are visible as a multitude of minute flecks distributed more or less evenly over all parts of both lungs. The resulting pulmonary shadow has been described variously as having a granular mottled marbled or stippled appearance. To me it seems to resemble a sponge the texture of which

varies from exceedingly fine to moderately coarse (figure 4)

Despite the almost pathognomonic evidence afforded by roentgen examination, dependence on it should not be absolute. Of diseases which may enter into the roentgenologic differential diagnosis the most common are malignant miliary metastasis and pneumoconiosis, particularly that produced by organic dust. Their chief marks of distinction are the following. Miliary metastatic lesions, although small, are very diverse in size, commonly denser than miliary tubercles, and most nu-

merous in the lower two-thirds of the lung. Pneumoconiosis ordinarily spares the apexes and is most manifest about the hilum; the individual lesions are likely to be larger, more irregular in size and shape, and denser than miliary tubercles. Accordingly, the examiner usually can venture a specific diagnosis, but prudence demands that it have clinical approval.

COMMENT

I am aware that this appraisal of the capabilities of the roentgen rays in the diagnosis of early pulmonary tubercu-



Figure 4. Miliary tuberculosis. The left image is a frontal view and the right image is a lateral view. Both illustrate the appearance of miliary tubercles on roentgenograms.

losis may seem unduly conservative to many who have implicit confidence in the roentgenologic examination, or may appear unduly liberal to the smaller number who are skeptical of the method. To the skeptics it may be pointed out again that without employment of roentgen rays as a routine, most of the truly early cases will escape recognition. Indeed, as a single rapid method for the definite revelation of the lesion, the determination of its probable nature, and even the estimation of its activity, I do believe that the roentgenologic examination is not surpassed by any other. Nevertheless, I have dwelt on its limitations because there is a prevalent tendency toward unquestioning reliance on laboratory tests. Although this flattering faith has been a

stimulus to roentgenologic progress, it has sometimes led the roentgenologist into incautious or unqualified interpretations. It has been difficult to learn that the normal chest has a wide range of variations, and that not all adventitious shadows are significant of present disease. Consequently the novice, and sometimes even the expert, are inclined to the diagnosis of tuberculosis when none exists. Many sound or nontuberculous persons have been sent to sanitariums on the basis of a roentgenologic opinion which the clinician failed to verify. In short, while the roentgen rays have brilliantly illuminated the field, the clinician still is obliged to study all the landmarks critically before he assents to a diagnosis so grave as that of tuberculosis.

REFERENCES

¹SAMPSON, H. L., and BROWN, L. The value of the roentgenologic examination in pulmonary tuberculosis, *Am Jr Roentgenol and Radium Therap*, 1931, xlv, 209-219.

²WEBB, G. B. The early diagnosis and early cure of pulmonary tuberculosis, *Jr Am Med Assoc*, 1929, xci, 1811-1813.

Medical Men Who Have Attained Fame in Other Fields of Endeavor

III. Medical Humorists. IV. Medical Men as Inventors. V. Medical Men as Explorers

By ERNEST WEINFELD, B S , M D , *New Orleans, La.*

III. MEDICAL HUMORISTS

SAAVEDRA Miguel de Cervantes (1547-1616) the greatest of Spanish writers, bent upon the alleviation of all the ills of mankind, was a doctor in very truth. He early commenced writing verses, and his pastoral, "Fílana", attracted the attention of Cardinal Acquaviva whom he accompanied to Italy as page. In 1570 when serving in the war against the Turks and African corsairs, he lost the use of his left hand. In 1583 he retired from service and recommenced his literary work, publishing in 1584 his pastoral "Galatea". He lived by writing for the stage, to which he contributed between twenty and thirty plays only two of which have

survived. In 1605 he produced the first part of Don Quixote and it had a hearty reception from the beginning among the populace, though not among the cultured classes. Between 1613 and his death were published his twelve "Exemplary Tales", "Journey to Parnassus" and eight new dramas. The second part of "Don Quixote" was also completed during these years and it is the masterpiece through which his fame lives.

Francois Rabelais (1490-1553) was at first a monk, but having been punished for some indecorous behavior, he quitted the Benedictine order, studied medicine at Montpellier, and later practiced as a physician. In 1532 he went to Lyons as hospital physician. In 1536 Rabelais obtained from the pope absolution for the violation of his monastic vows and permission to practice medicine and to hold benefices. During most of 1546 and part of 1547 he was physician to the town of Metz. Rabelais was the author of several books but the only one by which he is known is the romance called, "The Lives, Heroic Deeds, and Sayings of Gargantua and Pantegruel", an extravagant satire upon monks, priests, popes and pedants, in which much obscenity

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Note by Editor: Previous items in this series were I. Medical Men as Musicians, Vol. I, No. 1, 1930, pp. 1037-1054, and II. Medical Men as Poets, Vol. I, No. 2, 1930, pp. 127-128. Dr. Weinfeld had planned a third item, "Medical Men as Novelists," but it was not published. He had written a number of articles on the history of medicine and the history of the medical profession. He had also written a number of articles on the history of the medical profession. He had also written a number of articles on the history of the medical profession.

and absurdity are blended with learning, wit and humor Rabelais made one of the first Latin translations of the aphorisms of Hippocrates (Lyons, 1532) He was the first to lecture on medicine at Montpellier with the Greek text before him

Tobias Smollet (1721-1771) was educated in Dumbarton and at Glasgow Universities where he studied medicine After some years of apprenticeship with a surgeon, a Dr John Gordon, he went to London His interest, however, was rather in literature than in surgery and in 1739 made an attempt, but was unsuccessful in having his tragedy "The Regicide" performed After some years' service as surgeon's mate on board the Cumberland, he returned to England and again took up literature The first of his picaresque novels, "Roderick Random", appeared in 1748, and its success was immediate and great His second novel, "The Adventures of Peregrine Pickle" (1751), was even more successful He practiced as a physician at Bath, and in 1753 returned to London, gave himself up to literature and wrote "Ferdinand Count Fathoms" He made a lively but inaccurate version of "Don Quixote" (1755), published a "History of England" in four volumes (1757), and "Sir Lancelot Greaves" (1760), a weak imitation of "Don Quixote" After a tour of Italy Smollet published his "Travels" In 1769 he produced his coarse satire "The History and Adventure of an Atom", dealing with politics in England during the previous fifteen years In 1771 he wrote his masterpiece, "The Expedition of Humphrey Clinker"

Oliver Goldsmith* (1728 - 1774) went to Edinburgh to study medicine Here he remained eighteen months, during which time he acquired some slight knowledge of chemistry and natural history At the end of this period he went to Leyden, where he studied for nearly a year, and afterward he wandered over a large part of France, Germany, Switzerland and Italy He had no money to pay his expenses during his walking tour, but his kindness and humor won him friends everywhere, and his skillful playing of the flute gained him a scanty living While at Padua he took a medical degree He returned to England in 1756 where he commenced practice as a physician, in which he was unsuccessful He then entered the field of letters and his first work to attract attention was an "Inquiry into the Present State of Polite Learning in Europe" (1759) To this succeeded, "The Citizen of the World" a "Life of Beau Nash" and a "History of England" Becoming acquainted with Dr Johnson in 1761, the latter introduced Goldsmith to the Literary Club In 1764 appeared "The Traveler" which at once placed Goldsmith in the front rank of English authors Two years afterward appeared the "Vicar of Wakefield" Following in rapid succession came "The Good-Natured Man" (1767) "History of Rome" (1768) and the exquisite poem "The Deserted Village" (1770) In 1773, his immortal comedy of "She Stoops to Conquer or Mistaken for a Night" took the public by storm He

*See also Review of Oliver Goldsmith, M.D., and His Works, by J. G. Cooper, 1844—Editor]

other works are "Grecian History" (1774), "Retaliation" a serio-comic poem (1774), and "History of Animated Nature" which he did not live to finish. Washington Irving has written a remarkably sympathetic biography of Goldsmith.

Charles Jones Lever (1806-72) graduated in arts at Trinity College, Dublin, in 1827, and in medicine in 1831, taking his doctor's degree a little later at Gottingen. He then returned to Ireland to practice. In 1834, he contributed his first paper to the newly-started "Dublin University Magazine" of which he became editor in 1842. The first chapter of "Harry Lorrequer" appeared in that magazine in 1837. Meanwhile he was attached as physician to the British legation at Brussels, where he practiced for three years. During his three years editorship of the "Dublin University Magazine" he resided near Dublin, and afterwards lived on the Continent, devoting himself to fiction writing. "Charles O'Malley", "Tom Burke", and "Jack Hinton" are representative novels and in a class by themselves. He also wrote "Arthur O'Leary" and "Roland Cashel".

Oliver Wendell Holmes (1809-94) graduated from Harvard in 1829, in the class which he himself made famous in later years by his yearly poems at its reunions. After studying law for a time, he turned to medicine, at first with little seriousness. He became deeply interested, however, and in 1832, during which he studied in London, he was most industrious. His first medical paper of M.D. was published in 1835 and he settled down to practice in Boston. While

yet in college, Holmes wrote numerous poems including "The Spectre Pig" and "The Height of the Ridiculous". Following his graduation from Harvard he wrote "Old Ironsides". In 1839 he was given a position as lecturer on anatomy and physiology in Dartmouth College and in 1847 gave up his practice entirely and became professor of anatomy at the Harvard Medical School, a position he filled until 1882. Various medical papers, some of which were of great importance in the profession, such as "On the Contagiousness of Puerperal Fever" (1843) and "Puerperal Fever as a Private Pestilence" (1855) came from Holmes' pen from time to time, and his poems written to celebrate every special occasion in his beloved city of Boston made him locally famous as a wit. It was not until the founding of the "Atlantic Monthly" in 1857, however, that Holmes became widely famous. He contributed his papers "The Autocrat of the Breakfast Table" which are up to the present day considered his masterpiece. His first series was followed by "The Professor at the Breakfast Table" and later by "The Poet at the Breakfast Table". He wrote three novels, "Elsie Venner, A Romance of Destiny", "The Guardian Angel" and "A Mortal Antipathy". After a visit to Europe in 1886 appeared "Our Hundred Days in Europe" and when Holmes was eighty, he wrote a final autocrat series under the title of "Over the Teacups". Among Holmes' best poems may be mentioned "The Chambered Nautilus", "The Last Leaf", and the "The Wounded Hussar".

IV MEDICAL MEN AS INVENTORS

Joseph Ignace Guillotine (1738-1814) went to Paris, where he practiced medicine with such success as to win recognition as one of the foremost physicians of the day. When the Revolution broke out, he became one of its ardent supporters and suggested that a decapitating machine be used in inflicting the death penalty. After the rise of Napoleon he resumed his practice in Paris where he was one of the earliest and most earnest champions of vaccination.

Richard Jordan Gatling (1818-1903) graduated from the Ohio Medical College in 1850. He assisted his father in perfecting a machine for sowing cotton seed and another for thinning out cotton plants. In 1850 he invented a double acting hemp brake and in 1857 a steam plow. His principal invention and the one by which he became famous was the revolving machine gun which bears his name (1861). In 1886 he invented a new gun metal of steel and aluminum.

Rufus Henry Gilbert (1832-85), after graduating at the College of Physicians and Surgeons in New York City, began medical practice at Corning, N. Y. At the outbreak of the Civil War he became a surgeon in the Duryea Zouaves (Fifth New York Infantry) and rose to be medical director and superintendent of the Central Railroad of New Jersey. Gilbert was appointed superintendent and medical director of the United States army hospitals. Owing to the failure of his health during the war he abandoned his profession and engaged in the railroad business making a special study of the needs of rapid transit in New

York. The result was the erection (1878) of the Sixth Avenue Elevated Railway in that city.

Alexander Graham Bell (1847-1922) received his medical education at the University College, London, and the London University. In Elgin he was for two years resident master and teacher of elocution and music. He was greatly interested in his father's system of instruction of the deaf and dumb and in 1872 he became professor of vocal physiology in Boston University. Among his most important inventions are the harmonic multiple telegraph (1874) the fundamental method that underlies the electric transmission of speech to any part of the world (1895), the magneto-electric speaking telephone (1875), the photophone for transmitting speech and other sounds to a distance by means of a beam of light (1880), an induction-balance with magneto-electric telephone for painlessly locating bullets or other metallic masses lodged in the human body (1881), the telephone probe to determine the position of bullets or other metallic masses lodged in the human body (1881), the spectrophone for determining the range of audibility of different substances in the spectrum (1881), joint invention of the graphophone, tetrahedral kites (1903), joint inventor of a number of improvements designed to promote aerial locomotion.

Carl Auer von Welsbach (1858-) attended the University of Vienna and at Heidelberg (1880-82). In 1885 he discovered two new elements "thorium" and "neodymium" and invented the incandescent gas lamp known by his name. He received the

osmium incandescent electric lamp in 1898, and in 1907 discovered another new element known as "lutecium"

V MEDICAL MEN AS EXPLORERS

David Livingstone (1813-73) was a graduate of the Faculty of Physicians and Surgeons of Glasgow Under the auspices of the London Missionary Society he went in 1840 as medical missionary to South Africa He discovered the Victoria Falls of the Zambezi in 1855 From 1858 until his death, he prosecuted his labors as explorer and missionary in Africa

Elisha Kent Kane (1820-57) obtained the degree of M D at the University of Pennsylvania in 1842 He was attached as surgeon to the American mission to China and afterwards visited India, Egypt, and Greece In 1850 Kane joined the Ginnell Expedition, as medical and scientific member, in the unsuccessful search for Sir John Franklin His fame as an Arctic explorer rests on his second expedition, in search of Franklin in 1853-55 He sailed from New York in the brig "Advance" and reached lat 78°

41' N, the point farthest north attained up to that time by a sailing vessel

Hays, who accompanied Kane, was also a physician

Sir Wilfred Thomason Grenfell (1865-) graduated in medicine at London Hospital In 1889, under the auspices of the Royal National Mission to Deep Sea Fishermen, he equipped a hospital ship to accompany the fishing fleets from the North Sea ports to Iceland Three years later he went to Labrador and Newfoundland, where he established hospitals at many points along the coast He wrote many books, chief of which are "Off the Rocks" (1906), "Down to the Sea" (1910), "Down North on the Labrador" (1911), "The Adventures of Life" (1912)

Jean Baptiste Etienne Auguste Charcot (1867-) was educated in Paris and after graduating in medicine, was attached to several important hospitals In 1903 he began a series of antarctic explorations in the region of the South Pole His published writings are "France at the South Pole" and "Around the South Pole".

Editorial

THE COMPARATIVE COST OF MEDICAL JOURNALS

Faced with yearly deficits in the portion of its budget devoted to the purchase of medical periodicals, the Library of the College of Physicians and Surgeons of Columbia University undertook an analytical study¹ of the costs of the various medical journals purchased. It was soon found that the deficits were due in large measure to the impossibility of accurately determining the cost of certain periodicals in advance. While no such difficulty was encountered with the allowances for American, British or French journals, the estimates for German periodicals were frequently inaccurate. Many German medical publications are priced by the volume or by the part as issued, and in these days when there is such an urge to publish, the temptation to multiply volumes is very great. It is unfortunate that the German publishers do not adopt the fixed annual subscription plan. This would make it possible to regulate production and curb extravagant charges. Not only are several volumes crowded into one year but supplementary volumes, *Festschriften*, *Beihefte*, *Abhandlungen*, etc., are added, all at further increase in cost. The rank and file of American

medical readers must look to our libraries for these journals, and the libraries are naturally very desirous that their files should be kept intact. Present prices, however, are forcing cancellation in many instances, and with cancellations, other things being equal, prices must rise still higher for the cost of production is distributed over a smaller number of purchasers. During the year 1930-1931 the cost of certain important German medical periodicals was as follows: *Archiv f Dermatologie*, \$92.25, *Archiv f Psychiatrie*, \$103.57, *Deutsche Zeitschrift f Chirurgie*, \$62.88, *Strahlentherapie*, \$70.23, *Virchow's Archiv*, \$111.98, and *Zeitschrift f klinische Medizin*, \$74.55. If domestic subscription lists have fallen so low that foreign subscribers must be asked to pay such prices as those just quoted, it is high time that production costs were cut drastically. Material must be condensed and the number of pages and volumes reduced. Otherwise the present trend will prove to be suicidal. It would be a deplorable situation if the sequence of truly great journals with many decades of usefulness should be interrupted. Not all German medical periodicals fall into the price range quoted but the average annual cost of 88 of them received by the Library of the College of Physicians and Surgeons was \$36.11, while the average annual cost of 73 titles of American origin was \$7.91.

¹ROBERT, ALFRED L., and SCHATTENBERG, HANS H. The comparative cost of medical journals, *BULL. MED. LIBRARY ASSOC.*, 1932, no. 22, 140-155.

The cost per page affords a method for the private subscriber as well as for the library to arrive at comparative costs of periodicals. For a number of reasons this method is crude and inaccurate. Differences in size of page, quality of paper, number and type of illustrations and in the extent to which the subscription list is relieved of the necessity of carrying the full cost of production by endowments, subsidies, or income from advertising are factors—and there are many others—which enter into the cost per page. Since many of the operations in the production of a periodical are constant regardless of the number of copies issued, it follows that the cost per page can be lowered, either by reduction in the subscription price or by increase in the number of pages, as the list of subscribers grows. It is not surprising, therefore, that the Journal of the American Medical Association had a per page cost in 1930-1931 of but 0.16 cents. Returning to the national groups previously considered, the average cost per page of 88 German medical periodicals was found to be 1.88 cents while 73 American items had an

average cost per page of 0.58 cents. It is a source of satisfaction to find that the ANNALS OF INTERNAL MEDICINE was placed in the hands of its readers during that year at a cost of but 0.43 cents per page, well below the average of the American journals as a group. Even then it is not the lowest priced journal in its field, although it might be found to be such if the unit cost were weighted in respect to number and quality of illustrations used. The ANNALS will never be published for profit. In fact, it has required a subsidy from the general funds of the American College of Physicians in practically every year of its existence. With a growing subscription list, however, it should soon be not only self-sustaining but also in position to reduce the cost per page as well. That the price of subscriptions to our American journals is based on an annual volume assures the purchaser a fixed limit to his obligation and necessitates a fixed limit to the total output. It would be to the ultimate advantage of all medical libraries and of their patrons if the application of this system were made worldwide.

Abstracts

Dissection of the Aorta with Report of a Case. P. G. F. Smyth, M.D. *Ann. Int. Med.* Vol. 16, 1932, Nov., 15.

The following principles are applied to both the gross and microscopic study of the aorta: (1) the gross study of the aorta is made in the following order: (a) the external surface, (b) the internal surface, (c) the lumen, (d) the wall, (e) the branches, (f) the base, (g) the arch, (h) the descending aorta, (i) the abdominal aorta, (j) the iliac arteries, (k) the common iliac arteries, (l) the external iliac arteries, (m) the internal iliac arteries, (n) the common iliac veins, (o) the external iliac veins, (p) the internal iliac veins, (q) the common iliac lymphatics, (r) the external iliac lymphatics, (s) the internal iliac lymphatics, (t) the common iliac lymphatics, (u) the external iliac lymphatics, (v) the internal iliac lymphatics, (w) the common iliac lymphatics, (x) the external iliac lymphatics, (y) the internal iliac lymphatics, (z) the common iliac lymphatics.

the three examples described in this paper, in the first, which occurred in a man 19 years of age, the occlusion was complete and death resulted from rupture of the aorta. The second was in a man, aged 38 years, in whom the lumen of the aorta was reduced to a diameter of about 2 mm; death being due to cardiac decompensation. The third patient was a girl, aged 12 years. The diameter of the aorta at the point of rupture was 1.5 cm. Death was due to

chronic nephritis and pneumonia. No one of these cases was diagnosed as to the coarctation during life. With the condition borne in mind, such findings as cardiac hypertrophy, widening of the aortic arch, evidences of arterial collateral circulation, retarded femoral pulse, and a systolic murmur over the major collateral trunks may make the diagnosis possible.

The Effect of Cabbage Feeding on the Morphology of the Thyroid of Rabbits By ISOLDE T. ZECKWER, M.D. (Am Jr Path, 1932, viii, 235-244)

Feeding winter cabbage in the early part of 1931 to 17 rabbits for periods up to 114 days produced hyperplasia of the thyroid, but in only two instances were enlargements to more than twice the normal weight obtained. The microscopic changes were more conspicuous than the gross enlargement. The data obtained support the view of Webster, Marine and Cipra that there is an annual variation in the goiterogenic agent in cabbage, as well as seasonal differences and differences in the susceptibility of individual rabbits.

Cabbage and Goiter in Carpathian Ruthenia. A Contribution to Ethnic Pathology By Prof. V. SUK, M.D., Ph.D. (Anthropologie, Prague, 1931, ix, 1-6)

Goiter occurs endemically in many parts of the Carpathian Highlands, and the worst goiter centers are found in those poor villages where, during the unfavorable months of the year, more than two thirds of the population live to a great extent on cabbage, with the addition of potatoes, corn bread and oats. How great a part cabbage, which is utilized as boiled *sauerkraut* plays in the dietary is indicated by the fact that a family of eight members may pickle as much as 1100 pounds for their own use. Examination of the children in this region

showed a much higher incidence of goiter in the villages using excessive amounts of cabbage. This difference was especially evident among girls. Whereas 26.5 per cent of all the girls examined were without goiter, only 7.9 per cent of the girls in three villages using excessive amounts of cabbage were free from thyroid enlargement. Of all the girls, 9.4 per cent showed marked thyroid enlargement. For the three villages using much cabbage, the comparable figure was 15.8 per cent.

Torula Infection. A Review and Report of Two Cases By JAMES W. WATTS, M.D. (Am Jr Path, 1932, viii, 167-192)

Since Stoddard and Cutler pointed out the necessity of bearing torula infection in mind in patients with increased intracranial pressure without localizing signs, chronic meningitis, or other obscure cerebral conditions, the number of cases recognized has steadily increased. The first of the two here reported was in a woman, 32 years of age, in whom the infection was generalized although the symptoms were almost entirely cerebral. At autopsy a remarkable collection of pathological changes was found in the brain: diffuse meningitis, granulomas in the meninges, marked endarteritis and proliferation of adventitial elements of the meningeal vessels, an infarct in the pons, areas of softening in the cerebellum and various diffuse degenerative parenchymatous lesions. The second patient was a woman, 48 years of age, whose early complaints were headache, weakness and coldness of the extremities, inability to speak and difficulty in swallowing. At autopsy numerous cystic cavities from 1 to 8 mm in diameter were found in the brain. This case therefore corresponds to the embolic type of lesions as classified by Freeman. The respiratory tract is probably the portal of entry in most cases.

Reviews

A Text-book of X-Ray Therapeutics By ROBERT KNOX, completed and edited by WALTER M. LEVITT of the X-ray Department of St Bartholomew's Hospital, London, England. 250 pages, 106 illustrations. The Macmillan Company, New York City, 1932. Price, \$7.00.

At the time of his death Dr. Knox was engaged in the preparation of a comprehensive volume dealing with every branch of treatment by means of physical agents. However, only the sections concerning x-ray therapy were completed. These constitute an authoritative treatise on this subject as well as a memento of the work to which a great British radiologist devoted his energies for so many years. Dr. Levitt has very efficiently brought the text-book up to date, preserving the spirit of Dr. Knox's opinions on dosage and treatment, and keeping the balance between the claims of the more conservative therapists and the intensive methods of what might be called the newer school. Eight of the twenty chapters are entirely the work of Dr. Levitt. The subjects discussed are as follows: the effect of x-ray on tissues, the physics of x-ray therapy, x-ray measurements and dosage, the use of filters in x-ray therapy, with a description of the tubes and various types of high tension generators, the principles on which x-ray technique is based. About half of the text is devoted to these subjects, while the remainder is given over to a discussion of the various diseases in which the x-ray is used as a therapeutic measure. From the pathologist and the radiologist will be required a careful study of the anatomy of the various organs of the body, and particularly of the nervous system. The representation of the nervous system in the text has been particularly good, and the illustrations of the various organs of the body are of a high standard. The book is a valuable addition to the library of the radiologist and the pathologist.

The arrangement of the book is thoroughly logical, and the later chapters show a definite development from the physical and biological groundwork supplied in previous ones. The arrangement is excellent due to the careful outline and presentation of subject matter by organs and systems. A well chosen reference bibliography includes many classical articles which are of real value to the therapeutic radiologist. The book can be highly recommended as an excellent text for those who wish to learn some of the fundamental principles of x-ray therapy from a master. H. W. J.

Cytology and Cellular Pathology of the Nervous System. [By twenty-six contributors.] Edited by WILDER PIERCE, Professor of Neurology and Neurosurgery, McGill University, Montreal. In three volumes. xiv + 1267 pages; 886 illustrations (15 in color). Paul B. Hoeber, Inc., New York City, 1932. Price, three volumes, \$30.00.

This beautifully printed work, in three volumes of convenient size, is uniform in style with *Special Pathology*, edited by E. V. Cowdry, and with McClung's *Handbook of Microscopical Technique*. It is, in fact, a group of monographs by 26 internationally-known specialists in the fields of neurocytology and neuropathology. The first two volumes deal with the more fundamental considerations of normal and pathological cytology of the nervous system, while the third volume considers neoplasms, malformations and hematogenous reactions. This work should be found in every medical reference library. In such, and in the hands of the specialist and advanced student it will find its greatest use. As is recognized in the preface it is not a complete treatise of the pathology of the nervous system. The pathologist will find many of the chapters of great value as part of the general

eral discussion and not under separate headings. Thus the reader may search the index in vain for the names of certain familiar diseases. Perhaps subsequent volumes may be added to the present series to fill in these gaps, which are in part due to the incomplete state of our knowledge.

An Experimental and Clinical Study of Pain in the Pleura, Pericardium and Peritoneum. By JOSEPH A. CAPPS, M.D., F.A.C.P., Professor of Clinical Medicine, University of Chicago, with the collaboration of GEORGE H. COLEMAN, M.D., F.A.C.P., Assistant Professor of Medicine, Rush Medical College. Foreword by ANTON J. CARLSON, M.D., Ph.D., Chairman of the Department of Physiology, University of Chicago. iv + 99 pages, 33 illustrations. The Macmillan Company, New York City, 1932. Price \$3.00.

This book is the result of the wise application of the experimental method of scientific medicine to the daily practice of the art. When opportunity was offered by openings into the great body cavities, a silver wire passed through a hollow trocar was used to explore the pleural covering of lungs, chest wall and diaphragm, noting the presence or absence of pain and, when present, the exact location and character of the pain experienced. By a similar procedure the pericardial sac was explored when tapping for effusion, and likewise the peri-

toneum. The results of twenty years' application of this method are recorded in this small book. It thus becomes a unique contribution to the study of the significance of the localization of pain and of referred pain. It is compactly presented, simply written, and adequately illustrated. It should be read by all concerned with the diagnosis of disease of the chest and abdomen.

Clio Medica VII Medicine Among the American Indians. By ERIC STONE, M.D., xv + 139 pages, 17 illustrations. Paul B. Hoeber, Inc., New York City, 1932. Price, \$1.00.

To American readers the seventh book in the *Clio Medica* series will prove of unusual interest. The convenient size of these low-priced medical historical monographs has already been commented upon in this section of the *ANNALS*. The present volume deals with the medical theories and practices of the American Indian. The material is presented in a highly interesting manner and the reading of this small volume will, for many, correct erroneous ideas about the intimate life of the Indian prior to the coming of the white man. Moreover, Indian Medicine had its own important effect upon the medicine of the pioneer whites. Much of our medical folklore has an Indian background, and the Indian is said to have added 59 drugs to our modern pharmacopeia. This book is a good coat-pocket companion for a short railway journey.

College News Notes

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. H. Sheridan Baketel (Fellow), Jersey City, N. J.—1 reprint.

Dr. I. D. Bronfin (Fellow), Denver, Colo.—1 reprint.

Dr. John E. Grewe (Fellow), Cincinnati, Ohio—1 reprint.

Dr. Philip B. Matz (Fellow), Washington, D. C.—1 reprint.

Dr. Leon L. Solomon (Associate), Louisville, Ky.—5 reprints.

Dr. Edgar F. Kiser (Fellow), Indianapolis, Ind.—1 reprint.

Dr. Carl A. Vischer (Fellow), Philadelphia, Pa.—1 reprint.

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—2 reprints.

Dr. Norman Strauss (Associate), New York, N. Y.—1 reprint.

Dr. John Henry Peck (Fellow), Boston, Mass.—1 reprint.
Member, American Association of Anatomists, Secretary of the National Association of Anatomists.

At the recent annual meeting of the Medical Society of the State of North Carolina, at Winston-Salem, the following Fellows of the American College of Physicians gave papers as indicated

Dr Paul H Ringer, Asheville—"Modern Trends in the Management of Tuberculosis",

Dr S M Bittinger, Sanatorium—"A Brief Discussion, with Presentation of Several Types of Disease of the Lymphatic Glands Observed at the State Sanatorium",

Dr S D Craig, Winston-Salem—"Iodized Salt, its Common Usage and Results",

Dr I H Manning, Chapel Hill—"The Contributions of Biological Chemistry to Clinical Medicine",

Dr W T Rainey, Fayetteville—"Hypothyroidism",

Dr L B McBrayer, Southern Pines—"Tuberculosis in Early Adult Life and its Prevention",

Dr David T. Smith, Durham—"The Relation of Diet to Disease"

Dr O H Perry Pepper (Fellow), Philadelphia, Pa, was a guest speaker at this meeting

Dr M L Stevens (Fellow), Asheville, completed his term as President of the Medical Society of the State of North Carolina at its recent meeting

Dr Isaac H Manning (Fellow), Dean of the Medical Department of the University of North Carolina, Chapel Hill, was elected President-elect and will assume the office of President at the next annual meeting

Dr James B Bullitt (Fellow), Professor of Pediatrics at the University of North Carolina, was elected President of the North Carolina Association of Medicine at its thirty-third annual meeting at Wake Forest College

Dr Wm C B Miller (Fellow), Professor of Pediatrics, University of North Carolina, was elected President of the American College of Physicians at its thirty-third annual meeting at the University of California Medical School

lyn, was recently appointed Pediatrician to the Mary Immaculate Hospital, Jamaica, New York

Dr E Henry Jones (Fellow), Youngstown, Ohio, after pursuing postgraduate study in Dermatology and Syphilology, has abandoned his work in Internal Medicine and become Attending Dermatologist and Syphilologist to the Youngstown Hospital

Dr S Calvin Smith (Fellow), Philadelphia, Pa, spoke on "The Clinical Significance of the Irregular Pulse" at a joint meeting of the Columbia, Lycoming and Montour Counties Medical Societies held at Bloomsburg (Pa) Hospital, June 3

Dr Samuel M Feinberg (Fellow), Chicago, Ill, addressed the Carroll County Medical Society at Savanna, Ill, June 17, on "Respiratory Allergy"

Dr Curran Pope (Associate), Louisville, Ky, delivered an address before the Louisville Society of Medicine on June 2, his topic being "Personal Observation and Studies of Pyretotherapy"

Dr Louis F Bishop (Fellow) and Dr. Louis F Bishop, Jr (Fellow), both of New York City, addressed the American Therapeutic Society at its Baltimore meeting in May on "A Study of Vertigo or Syncope in Association with Cardiovascular Disease", with lantern slide demonstration of cases

Dr A W F Westhoff (Fellow), Richmond Hill, N.Y., was recently appointed Consultant to the Staff of the St Cecilia Women's Hospital, Brooklyn

Dr W McKim Marriott (Fellow), Dean and Professor of Pediatrics, Washington University School of Medicine, St Louis, has accepted the visiting lectureship at the University of California Medical School for 1932-33

Dr Sidney J Sherman (Fellow), San Francisco, Calif, has been made Associate Clinical Professor of Medicine at the University of California Medical School

Dr Oval N Bryan (Fellow), Nashville, Tenn, was elected President of the Middle Tennessee Medical Association at its meeting in May

Dr Lewellys F Barker (Fellow), Baltimore, Md, delivered the Commencement Address, May 31, at the University of Texas School of Medicine Commencement Day marked the dedication at the University of Texas School of Medicine of its three new buildings, including a medical laboratory, the John Sealy Hospital Outpatient Building and the Rebecca Sealy Residence for Nurses

The total cost of the three buildings was approximately \$2,500,000 The laboratory building contains laboratories for histology, embryology, pathology, anatomy and experimental surgery, in addition to a museum of surgical pathology, a museum of general pathology, a library and two large lecture halls The John Sealy Hospital Outpatient Building contains the administrative offices, x-ray department, surgical department, laboratories for basal metabolism and electrocardiography and clinics for ophthalmology, otolaryngology, obstetrics and gynecology, also laboratories, amphitheaters, mortuary room, animal houses, etc

Dr William A White (Fellow), Washington, D C, has been elected President of the International Congress on Mental Hygiene

Dr Charles F Martin (Master), Montreal, has been elected a Vice President

The second International Congress on Mental Hygiene will be held in Paris, France, during 1935

Dr Konrad E Birkhaug (Fellow), Associate Professor of Bacteriology, University of Rochester School of Medicine, Rochester, N Y, is in Paris studying at the Pasteur Institute He will also spend some time in the study of art A collection of water colors, bas-reliefs, masks and modeled figures by Dr Birkhaug were recently exhibited at the Art Center in Rochester

Dr Edward B Krumbhaar (Fellow), Philadelphia Pa and Dr Ward I McNeal (Fellow), New York, N Y, were

elected President and Vice President, respectively, of the American Society for Cancer Research at the recent meeting of that organization

Dr Joseph M King (Fellow), Los Angeles, was installed as President of the California Medical Association at its recent meeting in Pasadena

Dr Andrew C Gillis (Fellow), Professor of Neurology, University of Maryland School of Medicine, Dr Maurice C Pincoffs (Fellow), Professor of Medicine, University of Maryland, and Dr Robert H Riley (Fellow), Director of the Maryland State Department of Health, all of Baltimore, have been appointed Consultants to the Baltimore Health Department

Dr Marcus W Newcomb (Fellow) Browns Mills, N J, was elected a Vice President of the Medical Society of New Jersey at its annual session in Atlantic City, June 17

Dr Howard T Phillips (Fellow) Wheeling, W Va, read a paper on "Diagnosis and Treatment of Prevalent Skin Diseases" at Logan, W Va, before the Logan County Medical Society on August 19

At the annual meeting of the 6th District Medical Society held at Baton Rouge, La, on July 14, Dr Lester J Williams (Fellow), of Baton Rouge was elected President and Dr Cecil O Lorio (Fellow) of Baton Rouge was elected Secretary Treasurer

On the scientific program were Dr Philip H Jones (Fellow) of New Orleans whose subject was "Some Considerations in Relation to Scrums Proteins and Idioms" and Dr Cecil Lorio (Fellow) of Baton Rouge who presented a paper on "The Nervous System and His Difficulties"

"The Newer Synthetic Drugs in the Treatment of Biliary Diseases" was the subject of a paper by Dr Samuel Weiss (Fellow), New York City who presented it at the International Congress on Biliary Diseases at Vienna, France, Sept. 12-22, 1934

Dr Sidney A Slater (Fellow), Worthington, Minn, has been re-elected to the Directorate of the National Tuberculosis Association for a two year term

Dr William Egbert Robertson (Fellow), who has held the Chair of Medicine for many years at Temple University School of Medicine, has been appointed Emeritus Professor of Medicine, and will devote much of his time to medical research. Dr John A Kolmer will succeed Dr Robertson as Professor of Medicine, beginning with the autumn semester. Dr Kolmer has resigned as Professor of Pathology and Bacteriology at the Graduate School of Medicine of the University of Pennsylvania

At the regular meeting of the Western Oklahoma Medical Society, at Clinton, Okla, July 19, Dr Lea A Rielv (Fellow), Oklahoma City, and Dr Carroll M Pounders (Fellow), Oklahoma City, delivered addresses on "Some of the Complications of Diabetes" and "Diarrheas of Infants and Children", respectively

The University of Oklahoma conducted a postgraduate medical course in Degenerative Diseases for a period of four weeks during the summer. Dr Wann Langston (Fellow), Oklahoma City, offered the course in Generalized Arterial Disease, Hypertension and Myocardial Disease, Dr P T Bohan (Fellow), Kansas City, offered the course in Coronary Disease and Angina Pectoris, Dr C J Fishman (Fellow), Oklahoma City, offered the course in Vascular Disease of the Brain, Dr Lea A Rielv (Fellow), Oklahoma City, offered the course in Peripheral Vascular Disease and Chronic Rheumatic Disease, Dr A W White (Fellow), and Dr J T Martin (Fellow), both of Oklahoma City, offered the course in De-

generative Disease on Basis of Food Deficiencies, Pellegra, Pernicious Anemia, etc

Dr John H Peck (Fellow), Des Moines, Ia, headed a delegation of sixty American physicians to attend the Eighth Session of the International Union against Tuberculosis at the Hague and Amsterdam, September 6-9, 1932

Dr R H Kampmeier (Fellow), formerly Instructor in Internal Medicine at the University of Michigan Medical School, and more recently Internist at the Pueblo Clinic, Pueblo, Colo, has accepted an appointment as Assistant Professor of Medicine at the Louisiana State University Medical Center, New Orleans

Dr Frederick K Herpel (Fellow), West Palm Beach, Fla, was recently elected Vice President of the Florida Radiological Society

Dr Cecil O Lorio (Fellow), Baton Rouge, La, and Dr Maud Loeber (Fellow), New Orleans, La, were elected President and Secretary-Treasurer, respectively, of the Louisiana State Pediatric Society at its last meeting

Dr John A McIntosh (Fellow), San Antonio, Texas, was recently elected President of the Texas Neurological Society

Dr Charles G Jennings (Master), Detroit, Mich, in June was the recipient of the degree of Doctor of Science from the College of the City of Detroit

Dr Delvan MacGregor (Fellow), Wheeling, W Va, was elected President of the West Virginia Medical Association at its annual meeting in June

Artificial Fever Produced by the Short Wave Radio and Its Therapeutic Application

By C F TENNEY, M D, F A C P, *New York, N Y*

FOR the past fifteen years we have been interested in producing artificial fever as a therapeutic agent in the treatment of diseases of the peripheral circulation and arthritis by injecting a foreign protein intravenously following the work of Petersen, Miller, and Lusk. This injection produces a chill within thirty minutes to an hour, followed by a rise in temperature of from two to five degrees, this in turn is followed by a sweat. The blood changes are an increase in the number of white blood corpuscles, as well as in the polymorphonuclears, and a slight variation in the chemical constitution of the blood and in blood pressures. In the treatment with the foreign protein the majority of cases complain that the chill is the most uncomfortable part of the reaction. It is also with some anxiety that a foreign protein is injected into the circulation.

In former times fever was induced by the application of external heat to the body, such as the tub-bath, hot packs, the electric cabinet, thermal baths in so called healing waters, and mud packs taken from mineral springs.

Presented at the San Francisco meeting of the American College of Physicians, April 6, 1932

From the Medical Service of the Fifth Avenue Hospital, New York City

It is common practice in England today to wrap the patient in hot moist blankets, putting on more blankets to lessen heat radiation and thus produce an increase in body temperature.

Doctors have observed that patients suffering from a chronic ailment are sometimes benefited by an intercurrent infection associated with a chill, fever, and sweat.

A new adjunct in the treatment of paresis in the past ten years has been introduced by inoculating the patient with malarial parasites, which in turn produces chill, fever, and sweat but with the detrimental effect of destruction of the red blood corpuscles, the subsequent weakening of the patient and later having to cure the malaria. This treatment has however been most beneficial to these cases.

A newer form of producing hyperpyrexia is with the application of large diathermy plates to the trunk of the body, thus producing artificial fever. However, it is not a very comfortable jacket to wear.

Dr W R Whitney, Director of the Research Laboratory of the General Electric Company, Inc., of one of the men working in the field of short wave transmitter had this apparatus in his laboratory. He was interested in the treatment of paresis by Wagners method.

"Since 1928 special types of apparatus have been designed by the Research Laboratories of the General Electric Company and used experimentally in an endeavor to cause a fever in man rapidly, without great discomfort to the patient and to a degree high enough to be of value. The equipment used has been constructed on the same principle as a short wave radio transmitter, with the exception that the energy is concentrated between the two condenser plates instead of being directed from an aerial. The heating current is produced by a vacuum tube oscillator. This type of oscillator is composed of two sections operating at a frequency of approximately 10,000 to 14,000 kilocycles, the output of which is connected between the plates. The electrodes are mounted on a glass support and are surrounded and protected by a layer of oil. The electrodes are connected to a circuit which is controlled by a switch. The electrodes are connected to a circuit which is controlled by a switch. The electrodes are connected to a circuit which is controlled by a switch.

In the original use of the short wave radio machine in the research laboratories at Schenectady,¹ the University of Rochester,² the University of Toronto,³ the Albany Medical College,⁴ the New York State Psychiatric Institute,⁵ and the Baker Medical Clinic, Santa Barbara,⁶ considerable experimental

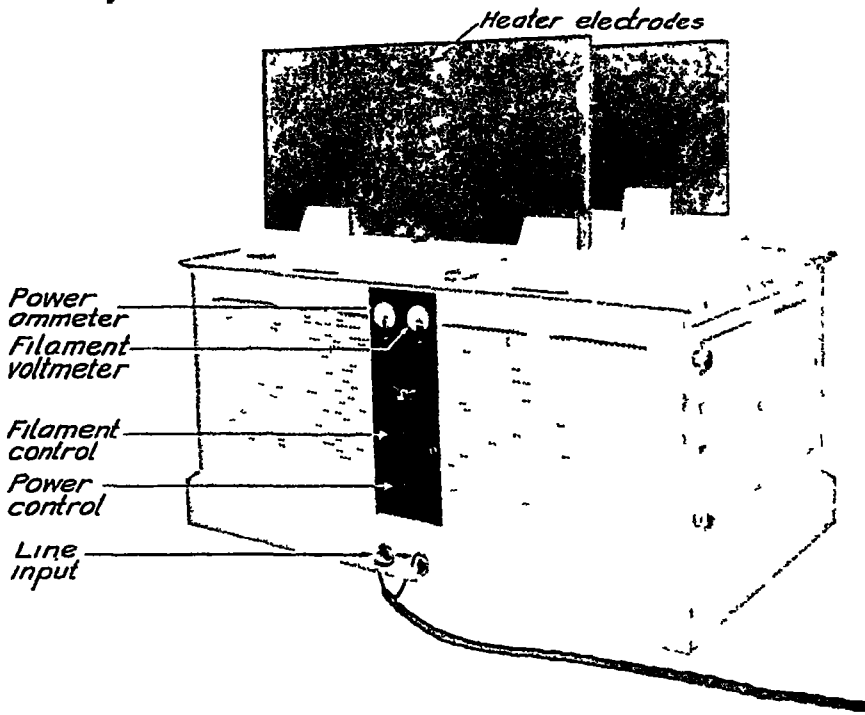


FIG 1 High-frequency heater for therapeutic use

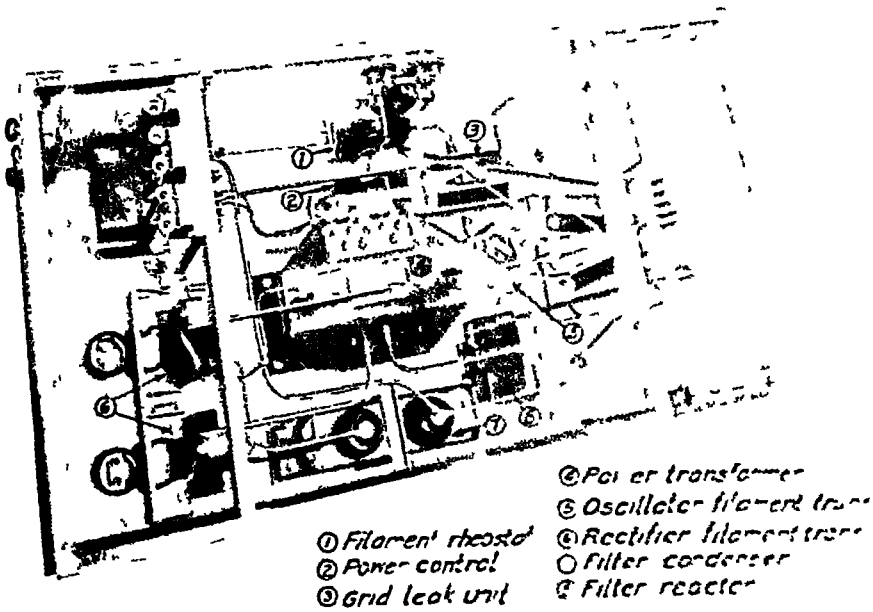


FIG 2 High-frequency heater without top to show internal components

work was done upon animals, as well as on the heating of fluids at different concentrations and on the heat effects upon bacteria. First efforts were directed toward demonstrating that the activity of the waves is harmless. This was done by subjecting white rats to a temperature of 105° daily for 120 days; these rats developed and had healthy litters the same as the controls, showing no apparent detrimental effects. Similar experiments were done on rabbits. Other research work was done to find out what happens when a solution such as sodium chloride in various concentrations was heated in the field of oscillation.

"It was found that with increasing concentrations of a simple electrolytic solution such as one of sodium chloride, the rate of rise in temperature increased rapidly from water to a maximum at a concentration of 0.0045 normal sodium chloride. In higher

concentrations it decreased. At 4.0 normal it was little more than that of pure water."

It is possible that the heating effect of these waves may also be selective in character and it has been proven by further experimentation in animals with the needle thermometer, that the temperature of the liver, heart, kidneys, spleen, and muscles, corresponds to the rectal temperature.

In the heating of the human body the patient is placed above the radio between the two plates and may be covered with a celotex cabinet with hot-air dryers blowing to evaporate the perspiration, or he may be placed between the plates wrapped in blankets.

We have found in our work that the patients are more comfortable and the temperature rise is more rapid if the following methods are observed in preparation for the treatment. Small



FIG. 1. Patient in position for treatment between plates.

superficial blisters may occur and are apparently due to the heat from the arc as well as to the drops of perspiration that are heated by the arcing. We request all our patients to buy a cotton and wool union suit that fits closely to all parts of the body, thus absorbing the perspiration in an even manner, they are then wrapped in a sheet, and blankets are snugly wrapped about them, covering the entire body except the head. If the patient complains of a burning sensation in any part of the body, the switch is turned off and the nurse strokes over that part so as to absorb the perspiration. The burning sensation ceases at once. Another point to keep in mind is the nervous anxiety of the patients in being confined in the blankets, especially after their temperature is 103° or above. Nausea may be complained of, but we have found it only in nervous patients. Still another point, but of less importance, is the placing of the wooden frame in front of the plates so as to prevent the possibility of anyone's coming within the wave length near them. In other words a person other than the patient may absorb considerable additional energy from the outfit if he comes too close to it, thus overloading the generating tubes.

The patient is placed on the canvas-stretched wooden frame between the plates so that the trunk of the body comes within the range of the plates. These are placed so that the waves oscillate through the body from one side to the other. The plate distance can be varied but as a rule has been kept at 30 inches. By applying the plates in this manner and having the body wrapped closely in blankets, it is heated rapidly

without causing great discomfort. We have raised the normal rectal temperature of 99.6° F to 104° and 106° in from 60 to 80 minutes. It is believed that the development of heat is due to the resistance of the body to the conduction of the current between the surface adjacent to the opposed plates as well as to the salt content of the blood.

In raising the temperature in the manner described, the greatest amount of resistance is found in the internal organs, such as the liver, heart, spleen and kidneys, due to their large blood supply.

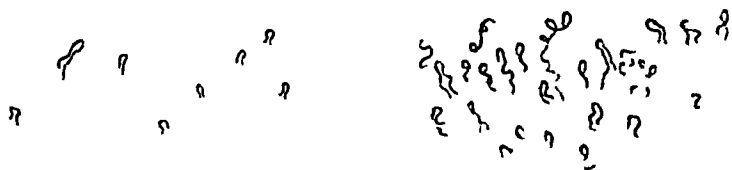
When the desired temperature is reached it may be maintained in several ways — (1) By increasing voltage, (2) by increasing plate distance, (3) by applying more blankets. When this temperature is reached we remove the patient in the blankets to his bed, placing more blankets and hot water bags about him so that the heat may be maintained from three to four hours longer, or we placed shellacked paper cabinets heated with electric light bulbs over the patient. In this way we may raise the body temperature even higher. The temperature of a thin person rises more rapidly than that of a fat one.

It is necessary to read rectal temperatures at least every fifteen minutes after 103° is reached. It is particularly important that these temperatures be observed because if the patient should have a disturbance of the thermal center of the brain, the temperature might rise to 109° and death follow. If the temperature should go higher than desired after the patient is in bed, a hot bag may be applied to the head, the blankets are then gradually removed, a cool sponge bath is given, and if the

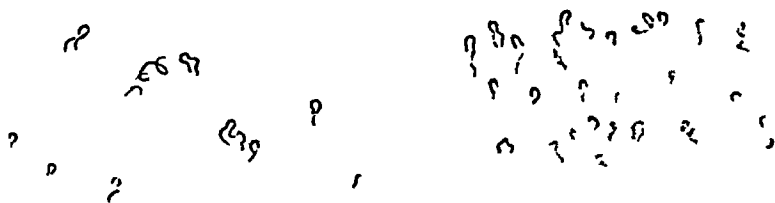
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GRAPHIC NURSING CHART					
NAME		ROOM No.		DOCTOR	
DATE		10/20/31		10/23/31	
DAY OF DISEASE					
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R		140 105		140 105	
U		130 104		130 104	
T		120 103		120 103	
A		110 102		110 102	
R		100 101		100 101	
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P		80 99		80 99	
M		70 98		70 98	
E		60 97		60 97	
T		50 96		50 96	
RESP		22 20		22 20	
PULSE		120 110		120 110	
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R		100 90		100 90	
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A		70 60		70 60	
R		60 50		60 50	
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temperature from the central origin continues to rise, cold colonic irrigations will control the situation. As the temperature falls and approaches normal, the blankets are gradually removed, a cool sponge bath is given followed by a crash towel massage. The patient is then placed in dry linen and is covered with light blankets after which he is very comfortable. Warm fluids should be given throughout the treatment to lessen dehydration. Warm orange-juice, water, and lemonade are given. Treatments, in the majority of cases, are given every other day. For the past two months we have been giving ambulatory treatments, the patient coming into the hospital in the morning, having his treatment, and going home that evening. On the alternate day a treatment with the local radio-thermy may be given for from thirty minutes to an hour.

We have done considerable work upon the blood chemistry, clotting factors, blood counts, viscosities, and blood sedimentation tests, both at the normal temperature and at various heights of fever produced by the high frequency heater. The chemical constitution of the blood as a rule shows only slight variations. The blood counts show a slight increase in the hemoglobin and red blood corpuscles, which is primarily due to dehydration but also due to stimulation of the blood forming organs as is shown by the younger forms of erythrocytes. According to Hinsie's work in the treatment of cases of general paralysis, "there is an increase of seventy-five per cent in the number of leukocytes as well as an increase in the staff cells which are the early forms of the polymorphonuclear neutrophils." This is due to circulatory stimulation of the bone marrow. The maximum in-



Left second finger before fever → Same finger at height of fever
Arthritic



Left third finger before fever → Same at height of fever
normal

FIG 5 Capillaries of nail beds before and during the fever. Patient with arthritis

crease comes, according to his findings, at about the ninth hour after treatment, returning to the normal level at about the twentieth hour. Our counts seem to indicate the same findings. The clotting factors show a definite increase in platelets. In no instance was blood viscosity increased at the height of fever in those cases where the loss of body fluids was replaced by a large fluid intake. Of thirty-three cases in which blood viscosities were taken, eighteen were arthritics. All of these ran a viscosity somewhat higher than normal. As the temperature rose in fourteen, viscosity dropped from 0.1 to 1.5 points, two cases remained unchanged and in four where fluid was not given there was an increase. One patient receiving a 5 per cent sodium chloride solution intravenously had a subnormal viscosity. In one case treated with sodium citrate intravenously before treatment, the viscosity was decidedly lowered. The blood sedimentation was faster and there was an increase in the blood plasma in these cases. The basal metabolic rate in one of the arthritic cases was minus twenty-nine before treatment; at a temperature of 104° it

was plus six, and after treatment, plus one.

In examining the circulation, microscopic study of the capillaries of the nail beds showed an increase in the size and number of capillaries during the height of the temperature. There is an increase in the oscillometer readings of the deep circulation, (table I) and an increase in the skin temperatures, as well as an increase in the size of the wheal in the histamine skin tests (table II) in some of the cases of occlusion of the blood vessels of the lower extremities. Another fact that we have noted is that the treatments seemed to have more of a tonic effect than a debilitating one even though the temperature is high and the sweating considerable. There is a loss in weight in the early treatments which is gained as the treatments progress.

SUMMARY

We have been very much encouraged in our work with the High Frequency Heater as an aid in treatment. Arthritis (table III) has become such an economic problem that any aid in the care of this disease is of great value. We

TABLE I
Oscillometer Readings—Deep Circulation

Before Treatment			At Height of Temperature			After Temperature Has Returned to Normal		
Left Leg	Right Leg	Blood Pressure	Left Leg	Blood Pressure	Right Leg	Left Leg	Blood Pressure	Right Leg
120	120	120	120	160	0	1/2	160	1/2
120	120	120	120	150	0	1	150	1/2
120	120	120	120	140	1/2	1 1/2	140	1/2
120	120	120	120	130	1/2	1 1/2	130	1 1/2
120	120	120	120	120	1/2	2	120	1
120	120	120	120	110	1/2	1 1/2	110	1
120	120	120	120	100	1/2	1	100	3/4
120	120	120	120	90	1/2	1	90	3/4
120	120	120	120	80	1/2	1/2	80	---
120	120	120	120	70	1/2	---	70	---

TABLE II
Mr A R, Histamine Test for Skin Circulation
Diagnosis Intermittent Claudication (Arteriosclerotic Type)

Before Radiotherapy—11 30 A M			After Radiotherapy—5 00 P M		
	Left Leg	Right Leg		Left Leg	Right Leg
Ankle	2	1	Ankle	3	2
Leg	3	2	Leg	3	3
Below knee	3	2	Below knee	3	3
Above knee	3	3	Above knee	3	3

CODE

- 0 = No reaction
1 = wheal only
2 = wheal with mild flare
3 = wheal with marked flare

think as Dr Ralph Pemberton does, that arthritis is in part a disease of the circulation and that any one of several infective agents may be the causative factor in many of the cases. Heat in almost any form is excellent. If a patient is undergoing a course of vaccine therapy under the direction of his physician and is referred to us for radiotherapy, the vaccine is continued. The greater number of our cases have been treated with radiotherapy and massage, with the preliminary step of removal of foci of infection.

In our use of the High Frequency Heater in the treatment of syphilis, we have treated primary, secondary, and tertiary cases in conjunction with the regular antileptic treatments. The results of the treatment (table IV) in the primary and secondary cases, have been good, the primary lesion and secondary rash disappeared with unusual rapidity. In some of the cases whose Wassermann reaction was strongly positive, after one treatment the reaction has been returned as weakly positive. Our best results have been obtained in the tertiary cases especially in those involving the central nervous system.

"Doctor Hinsie's observations on 136 patients with general paralysis, one-half of

whom had malarial treatment and the other half radiotherapy treatments, show that the clinical signs of improvement have been equal in both. The laboratory findings, however, do not show signs of improvement as rapidly in the radiotherapy treated cases as in the malarial. The explanation of this is that it takes longer for laboratory findings to change than it does for clinical manifestations."

If a temperature of 106° is maintained from two to four hours in cases of gonorrheal infection, such as urethritis, arthritis, and pelvic inflammatory disease, it acts almost as a specific. As the thermal death point of the gonococci is supposed to be around 104° , they are probably destroyed by the heat.

In diseases of the circulation of the lower extremities, we have used both the general and local forms of therapy. In the few cases of intermittent claudication of the arteriosclerotic type we have treated, there is improvement, pain comes on later in exercise, and there is an increase in the arc of the oscillometer readings. In thrombo-angitis obliterans in younger individuals we have not had sufficient time nor cases to draw definite conclusions. In three cases of Raynaud's disease treated, the results compare favorably with those of foreign section operations.

TABLE III
Results of Radiotherapy Treatments and Massage

ARTHRITIS 63	Hypertrophic 47	Symptom Free 3 Improved 38 Unimproved 6
	Atrophic 16	Symptom Free 4 Improved 10 Unimproved 2
BURSITIS 4	Without calcification 2	Symptom Free 1 Improved 1 Unimproved 0
	With calcification 2	Symptom Free 1 Improved 1 Unimproved 0
MYOSITIS 8	Symptom Free 2 Improved 6 Unimproved 0	
NEURITIS 5	Symptom Free 5 Improved 1 Unimproved 0	

TABLE IV

Radiothermy in the Treatment of Lues
In addition to regular antiluetic treatments, these patients received from 3 to 30 radiotherm treatments

NAME	DIAGNOSIS	DURATION	SYMPTOMS	PRESNT CONDITION
1 W B	Lues, 1st and 2nd stages	8 months	Primary and secondary rash, Wassermann 4 plus	Symptom free
2 J M	Lues, tabes dorsalis	5 years	Gastric crisis, loss deep reflexes	Improved
3 B A	Lues, 1st and 2nd stages	1 month	Primary and secondary rash	Symptom free
4 E G.	Lues, 1st and 2nd stages	2 months	Dark field 3 plus, secondary rash	Symptom free
5 W D	Lues, 1st and 2nd stages	2 months	Primary and secondary rash	Symptom free
6 E W	Lues, tabo-paresis	1 year	Spinal fluid 4 plus	Improved
7 M S	Lues, 2nd stage	6 months	Wassermann 4 plus Wassermann 1 plus	Improved
8 P R	Lues, congenital	Life	Blood Wassermann 4 plus spinal fluid 4 plus	Unimproved
9 H F	Lues 3rd stage	?	Charcot joint	Unimproved
10 C S	Lues, 2nd stage	6 months	Wassermann 4 plus Wassermann 1 plus	Improved
11 B T	Lues 3rd stage	12 years	Wassermann 4 plus	Unimproved
12 E M	Doubtful lues	?	Very nervous	Unimproved
13 J E	Lues, congenital	Life	Nerve deafness	Unimproved
14 W B	Tertiary lues	?	Mental confusion	Unimproved
15 E K	Tabo-paresis	3 years	Blurred vision, unsteady gait old fracture of femur	Improved
16 D A	Tabes dorsalis	2 years	Pains in legs	Improved
17 C R	Tabo-paresis	?	Pains in legs	Improved
18 H H	Tabes dorsalis	25 years	Ataxia loss of deep reflexes	Improved
19 M D	Tabes dorsalis	20 years	Ataxia loss of deep reflexes	Unimproved
20 D P	Lues	10 years	Disseminate sclerosis of cord	Unimproved
21 B D	Lues	10 years	Indigestion, anxiety	Improved
22 D K	Lues, 1st and 2nd stages (infectious)	3 months	Rash headache Dizziness, difficulty in walking tabetic gait urinary incontinence	Symptom free Improved
23 E L	Tabo-paresis	4 years	Lesion on penis	Symptom free
24 L S	Primary syphilis	2 months	Uncertainty of gait urinary incontinence	Improved
25 E S	Tabes dorsalis	7 years	Lesion on penis rash	Symptom free
26 C S	Primary and secondary syphilis	3 months	Blurred vision	Improved
27 J J	Interstitial keratitis	2½ years	Chancre rectum	Symptom free
28 L R	Primary syphilis	3 months	Chancre of penis	Symptom free
29 E R	Primary and secondary syphilis	3 weeks	Chancre of lip rash	Symptom free
30 A B	Primary syphilis	8 months	Pain in legs weakness of gait	Improved
31 O S	Tabo-paresis	?		

On the other eight cases, we have been unable to get full improvement

CONCLUSIONS

1 We feel that we are using a form of artificial fever which is less hazardous than that produced by intravenous injections, and these conclusions have been reached after giving over one thousand treatments

2 It is a form of fever which is entirely within the control of the operator, if kept below 107.°

3 There is very little discomfort to the patient

4 Application is simple

5 We believe that this method of producing artificial fever is superior to other methods, and that the therapeutic results obtained are better.

Laboratory studies were conducted by the following

Pauline VanAlstyne, tests on blood viscosity,

Charlotte Caduff, blood sedimentation tests,

Katherine Oblander, blood counts and blood chemistry

REFERENCES

¹CARPENTER, C M, and PAGL, A B The production of fever in man by short radio waves, Sci, 1930, lxxi, No 1844, 450-462

²HINSIE, L E, and CARPENTER, C M Radiothermic treatment of general paralysis, Psychiatric Quart, 1931, v, 215-224

³McLENNAN J C The heating effect of short radio waves, Jr Maryland Academy Sci, 1931, ii, No 1, 14-24

⁴McLENNAN, J C, and BURTON, A C Selective heating by short radio waves and its application to electrotherapy, Canad Jr Research, 1931, v, 550-566

⁵McLENNAN, J C, and BURTON, A C The heating of electrolytes in high frequency fields, Canad Jr Research, 1930, iii, 224-240

⁶KNUDSON, A, and SCHAIBLE, P J The effect of exposure to an ultrahigh frequency field on growth and on reproduction in the white rat, Arch Path, 1931, ii, 723-727

⁷HINSIE, L E, and BLALOCK, J R Leucocytes in general paralysis treated by radiotherapy, Psychiatric Quart, 1931, v, 432-440

⁸PFEMBERTON, R Arthritis and rheumatoid conditions, their nature and treatment, 1929, Lea & Febiger, Philadelphia

A Comparison of Orthodiagraphic and Teleroentgenographic Measurements of the Heart and Thorax

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ORTHODIAGRAPHY was first introduced by Moritz thirty years ago. In his first article on this subject (*Munch med Wchnschr*, No 29, July 17, 1900) he explains that because of the fact that roentgen rays originate from a point on the anti-cathode and from this point radially diverge, the shadow which they produce will necessarily be distorted in triangular proportion to the distance of the object from the anti-cathode. The teleroentgenogram will always be larger than the object. In order to overcome this error Moritz devised a method by which he could cut out all the rays except the true central or parallel ray. With this central ray he outlined the silhouette of the heart and chest wall. Since there is no divergence in the central ray as it is moved tangentially around the silhouette one obtains the exact size of the frontal plane of the heart and chest wall. For detailed description of the technique and apparatus used by Moritz one should consult the original article. Suffice it to say here that the tube was movable and that the outline of the shadow cast by the heart and chest wall from the central ray was directly recorded on the fluorescent screen.

In the early work on determination of the heart size by roentgen ray photography the distances of the patient from the tube were much less than the distances which are used today. Rosenfeld in 1897 used 40 cm., and Gotch in 1898, one meter. These distances were not satisfactory and therefore Kohler in 1905 introduced the use of the two meter distance (teleroentgenography). Even from this distance, however, the rays are not parallel when they reach the object studied and hence there is still some distortion. Van Zwaluwenburg stated that "Even at nine feet the shadow on the plate usually exceeds that of the orthodiagram by from 6 to 15 per cent. The same error appears in the outline of the chest wall." Hodges also expresses the opinion that "some distortion of the shadow exists at 9 feet".

All authorities agree that the orthodiagraphic measurements are more accurate than the teleroentgenographic with perfect technique in the use of both methods. Groedel has even gone so far as to say "But when we wish to determine the form, position, and size of the heart, observations made by the orthodiagraph are absolutely correct."

In spite of the recognition that the

thorities of the greater accuracy of the orthodiagram in actual measurements as compared to the teleroentgenogram (or "six or seven foot" plate or film) most physicians in this country do not appreciate this fact and are quite unfamiliar with the simplicity and value of the orthodiagraphic method. Hence we have made a brief study of the results of a comparison of orthodiagrams and teleroentgenograms of the heart and great vessels which we are presenting herewith.

Our series consists of twenty-two cases. Ten of these had hearts of normal size, ten had enlarged hearts, the twenty-first case was one of luetic aortic aneurysm and the twenty-second case was one of pericarditis with effusion.

For the sake of practical application of this study the orthodiagrams were made by ourselves* while the teleroentgenograms were made at the same time of day within a day or two in the ordinary routine manner by the X-ray Department of the Massachusetts General Hospital, and we would like herewith to express our thanks for the cooperation given us in this study. With closely controlled records made simultaneously by both methods in the same phase of respiration greater accuracy

and a nearer approach to theoretical expectations would be possible than we secured here, but the advantage of comparison of the two methods carried out independently and in a routine way would thereby have been lost.

The usual measurements were taken, that is, transverse diameter (T) which is the sum of the perpendicular distance from the midline to the extreme right border of the heart (MR) and similar distance to the extreme left heart border (ML), longitudinal diameter (L), width of the great vessels just above the heart shadow itself (GV), the internal horizontal diameter of the chest (Th), and the cardiothoracic ratio (CTR) which is determined by dividing the transverse diameter of the heart (T) by the internal transverse diameter of the thorax (Th). The cardiac areas (A) were computed with the use of a planimeter, these area measurements cannot be said to be free of error as the outline of the heart had to be established somewhat arbitrarily at the upper and lower borders by joining the ends of the right and left borders of the heart shadow by slightly convex lines. The teleroentgenograms were made with the customary technique, the target of the tube being seven feet from the photographic film with which the anterior chest wall of the subject was in contact. We, ourselves, made all the measurements on both orthodiagrams and teleroentgenograms.

The measurements of the entire series are given in the large table.

To determine how large an error may enter into the figures by simple variation in the measurements of the heart size and chest size of an individual repeated on different days we

*The orthodiagrams were made with the Reflex heart vertical fluoroscope with special attachment which rendered the heart shadow on a paper target by means of a camera lucida. The heart shadow was represented exactly as it appeared. There is a small error in the measurements of the heart shadow on the paper target, but this is not greater than the error in the measurements of the heart shadow on the teleroentgenogram.

orthodiagraphed two persons twice at an interval of one day in one instance and of three days in the other. As in the case of the routine study of the special series, we were careful to trace and measure as accurately as possible and under the same circumstances at the same time of day. The measurements in centimeters in these two individuals were as follows:

		MR	ML	T	L	GV	TH	CTR	ARI A
S McG	First day	38	90	128	132	50	24.5	52.2%	92.4
	Second day	37	92	129	135	50	24.4	52.8%	97.7
R P B	First day	38	75	113	132	40	23.0	49.1%	97.3
	Second day	38	75	113	132	40	22.8	49.5%	91.2

Thus it is evident that one may attain a high degree of accuracy in measurement. The least constant and therefore least satisfactory comparative measure-

ment proved to be that of area, this was in large part due undoubtedly to the need of filling in arbitrarily upper and lower borders of the heart shadow.

I THE NORMAL GROUP

The group of normal sized hearts is from healthy individuals (Figure 1 shows the tracings in Case 1.)

1 Transverse diameter. The trans-

verse diameter was greater by tele-roentgenography than by orthodiagraphy in all cases, the greatest difference being 1.4 cm., and the smallest differ-

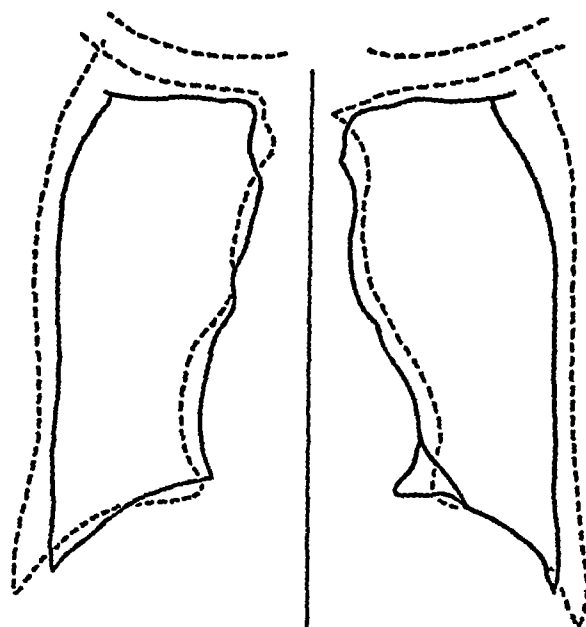


Figure 1, H.B.S. Group I, Case 1.

FIG 1 Orthodiagram (solid line) and tracing of telecentricogram (dotted line) of borders of heart, great vessels, clavicles, and diaphragm in the lateral walls of the thorax of H.B.S. Case 1 of Group I. The vertical midline is also represented. Records made during quiet respiration. For actual size. See table for measurements.

ence 0.4 cm. The teleroentgenogram averaged about 1 centimeter (0.9 cm) greater than the orthodiagram in the transverse diameter of the heart in these normal individuals

2. Median right (MR) The median right diameter by teleroentgenographic measurement was less than that by orthodiagraphic measurement four times, equal to the orthodiagraphic once, and greater five times, the greatest difference between the orthodiagram and the teleroentgenogram was 1.7 cm. The teleroentgenogram averaged 0.2 cm greater than the orthodiagram in this MR distance

3. Median left (ML) The teleroentgenogram showed a greater median left diameter in all except two cases. The least difference in measurements was when the teleroentgenogram was 0.2 cm less than the orthodiagram; the greatest was when the teleroentgenogram was 2.0 cm greater than the orthodiagram. The teleroentgenogram averaged 0.7 cm greater than the orthodiagram in the ML distance.

4. Longitudinal (L). The longitudinal diameter, i.e., from the point of junction of right auricle and aorta or superior vena cava to the apex, was found in each case to be greater by teleroentgenography than by orthodiagraphy, the greatest difference being 2.6 cm, the least 0.6 cm; the average was 1.5 cm

5. Great vessels (GV) The greatest transverse width across the heart was found in the anteroposterior projection and the teleroentgenographic measurement was greater than the orthodiagraphic measurement in all cases and by an average of 0.4 cm. The teleroentgenographic measurement was greater than the orthodiagraphic measurement in all cases and by an average of 0.4 cm.

(Th) we found a greater degree of difference in the results of the two methods, here the teleroentgenograms averaged 2.5 cm more than the orthodiagrams, and the teleroentgenograms gave larger measurements in every case.

7. Cardiothoracic ratio (CTR, that is, T divided by Th). The cardiothoracic ratio (percentage) in seven of the ten normal sized hearts presented a lesser value by teleroentgenogram but in the total of ten cases averaged only 0.9 per cent less than in the orthodiagram. The greatest difference occurred in a case which showed a cardiothoracic percentage by teleroentgenogram 3.3 per cent less than by orthodiagram

8. For the cardiac area (A) the square centimeter was chosen as the unit of measure and in all of the normal cases the teleroentgenographic area was larger than the orthodiagraphic. The greatest difference was of 41.0 sq. cm and occurred in two cases; the average difference was 22.2 sq. cm. Expressing this difference in terms of percentage of the orthodiagraphic area so that we may have a clearer idea of the comparison, we find that the area by teleroentgenogram was greater than that by orthodiagram by 44.0 per cent in an extreme case while the average difference in area size was 24.7 per cent

From these measurements in the normal cases it is evident that, as was to be expected, the greater the measurements the greater is their magnification by teleroentgenogram. The discrepancies in a few of the MR and ML measurements are to be accounted for by a failure in technique; that is, the measurements by orthodiagram and by teleroentgenogram were not made on the same

roentgenogram are taken without maintaining the heart in exactly the same position. A slight rotation or lack of exact centering will affect the relative lengths of MR and ML, without affecting T. Moreover, the teleroentgenograms were made at varying phases of quiet breathing and of the cycle of cardiac contraction while the orthodiagrams were drawn so far as possible in midrespiration and in a phase midway between systole and diastole, this may easily account at times for a discrepancy of a few millimeters. Finally it is not possible to make, in a practical way, measurements by either method that are exact to a millimeter or two, as indicated by comparing successive orthodiagrams or successive teleroentgenograms. This factor alone readily accounts for some of the individual discrepancies but the average

orthodiagraphic measurements are always less than the average teleroentgenographic measurements.

II GROUP OF ENLARGED HEARTS

Figure 2 shows the tracings of Case 1 of this group.

1 Transverse. In the enlarged hearts we found that the teleroentgenographic transverse measurements were greater in all but one of the ten cases, the least difference being 0.6 cm. and the greatest 1.8 cm., while the average showed T by orthodiagram less than that by teleroentgenogram by 1.1 cm.

2 Median right. The median right measurement as recorded by teleroentgenogram was greater than the orthodiagraphic measurement in seven cases, twice the two methods gave equal results and once the teleroentgenogram gave less. The greatest difference was

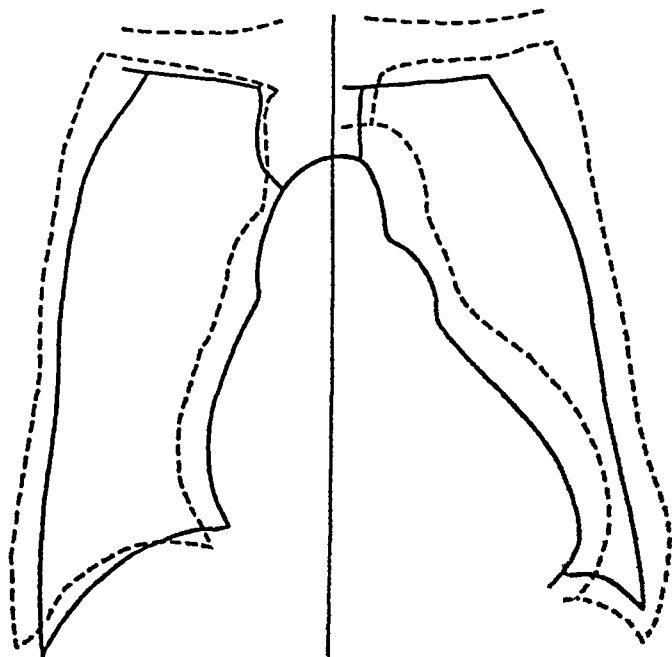


Figure 2. F. O. Group II, Case 1.

FIG. 2 Orthodiagram (solid line) and teleroentgenogram (dashed line) tracings of the heart silhouette of Case 1 of Group II taken during full inspiration. Reduced to $\frac{1}{4}$ actual size.

Group I, Normal Hearts

TABLE: Orthodiagraphic and Teleroentgenographic Measurements, in centimeters, of Cardiac Diameters and Areas, Width of Great Vessels, Internal Diameter of Thorax, and Cardio-Thoracic Ratios, in Series of Ten Normal Individuals and Twelve Cases with Cardiac, Aortic or Pericardial Enlargement

No	GROUP	TRANSVERSE			MIDIAN RIGHT			MIDIAN LEFT			LONGITUDINAL			GREAT VESSELS			THORAX			CARDIO-THORACIC RATIO													
		Cm			Cm			Cm			Cm			Cm			Cm			Orth		Tel		Diff		Orth		Tel		Diff		Percentage	
		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	Orth	Tel	Orth	Tel	Diff	Orth	Tel	Orth	Tel	Diff	Percentage			
1	43	10.5	11.9	+1.4	5.1	6.1	+1.0	5.4	5.8	+0.4	11.7	12.9	+1.2	5.2	6.3	+1.1	24.2	27.6	+3.4	10.5	11.9	24.2	27.6	-0.3	91	107	16	17.6					
2	46	10.5	13.4	+2.9	3.4	3.9	+0.5	9.2	9.9	+0.7	14.0	14.8	+0.8	5.6	5.3	-0.3	24.7	26.8	+2.1	12.6	13.8	24.7	26.8	+0.4	107	137	30	28.1					
3	42	13.1	14.5	+1.4	4.8	4.2	-0.6	8.3	10.3	+2.0	13.5	15.7	+2.2	5.6	5.5	-0.1	25.5	28.1	+2.6	13.1	14.5	25.5	28.1	+0.3	105	127	22	21.0					
4	49	11.7	12.8	+1.1	4.1	5.4	+1.3	7.6	7.4	-0.2	12.0	14.6	+2.6	5.2	4.9	-0.3	25.0	28.7	+3.7	11.7	12.8	25.0	28.7	-2.3	93	134	41	44.0					
5	47	10.5	12.0	+1.5	4.0	3.6	-0.4	5.5	6.4	+0.9	11.0	12.5	+1.5	4.2	4.0	-0.2	24.7	27.0	+2.3	9.5	10.0	24.7	27.0	-1.5	69	85	16	23.2					
6	48	12.1	12.9	+0.8	3.3	3.0	-0.3	8.8	9.9	+1.1	13.7	15.5	+1.8	4.7	5.0	+0.3	27.8	30.0	+2.2	12.1	12.9	27.8	30.0	-0.5	106	147	41	38.6					
7	48	9.7	10.4	+0.7	3.9	4.0	+0.1	5.8	6.4	+0.6	11.5	13.7	+2.2	4.5	4.7	+0.2	24.5	25.0	+0.5	9.7	10.4	24.5	25.0	+2.0	78	107	29	37.2					
8	44	7.3	8.2	+0.9	2.0	3.7	+1.7	5.3	4.5	-0.8	8.5	9.1	+0.6	3.0	3.6	+0.6	15.6	17.9	+2.3	7.3	8.2	15.6	17.9	-1.0	41	45	4	9.7					
9	45	9.9	10.3	+0.4	2.8	1.9	-0.9	7.1	8.4	+1.3	11.0	11.7	+0.7	3.4	4.3	+0.9	21.3	23.8	+2.5	9.9	10.3	21.3	23.8	-3.3	75	92	17	22.7					
10	44	11.9	12.5	+0.6	4.4	4.4	0	7.5	8.1	+0.6	13.0	14.7	+1.7	5.5	4.7	-0.8	27.2	30.5	+3.3	11.9	12.5	27.2	30.5	-2.8	115	121	6	5.2					
	AV	DIFF	+0.9		AV	DIFF	+0.24	AV	DIFF	+0.66	AV	DIFF	+1.53	AV	DIFF	+0.14	AV	DIFF	+2.49						AV	DIFF	-0.90	AV	DIFF	22.2	AV	DIFF	24.73

Group III, Special Cases

No.	TRAUS, 1957	MIDIAN RIGHT			MIDIAN LEFT			LONGITUDINAL			GREAT VESSELS			THORAX			CARDIO-THORACIC RATIO			CARDIAC AREAS (Sq Cm)					
		Tel	Diff	Orth	Tel	Diff	Orth	Tel	Diff	Orth	Tel	Diff	Orth	Tel	Diff	Orth	Tel	Diff	Orth	Tel	Diff	Orth			
		Cm			Cm			Cm			Cm			Cm			percentage			percentage					
GROUP III																									
1	114 129 111	20	1.7-0.3	9.7	11.2	+1.5	13.5	14.5	+1.0	10.2	10.8	+0.6	24.6	29.5	+4.9	11.8	12.9	11.3	12.9	94	113	81	20.2	8.7	
2	114 205 215 110	10.3	11.5-1.2	10.2	13.0	+2.8	16.5	19.2	+2.7	6.2	7.0	+0.8	22.2	27.2	+5.0	20.5	24.5	24.6	29.5	230	359	129	56.0		
3	114 124 136 112	1.2	5.2-4.0	8.2	8.4	+0.2	13.2	15.9	+2.7	7.0	7.3	+0.3	25.4	28.0	+2.6	12.4	13.6	12.4	13.6	90	107	17	18.9		
4	114 115 114	4.8	4.2-0.6	8.3	10.3	+2.0	13.5	15.7	+2.2	5.6	5.5	-0.1	25.5	28.1	+2.6	13.1	14.5	13.1	14.5	105	127	22	21.0		
5	113 121 108	3.6	4.0-0.4	7.7	8.1	+0.4	12.7	14.0	+1.3	5.0	5.5	+0.5	28.0	29.6	+1.6	11.3	12.1	11.3	12.1	88	129	41	46.5		
6	114 113 113	5.2	5.5-0.3	9.6	10.6	+1.0	16.0	16.6	+0.6	6.5	8.5	+2.0	25.0	27.0	+2.0	14.8	16.1	14.8	16.1	142	148	6	4.2		
																	94	19	7						
																	81	7				56.0			
																	230	129				18.9			
																	90	17				21.0			
																	105	22				46.5			
																	88	41				4.2			
																	142	6							

* Same case with pericardial effusion. * Area of heart above the line and area of aneurysm below the line
O Same case with heart measurements after pericardial paracentesis.
† 95 mm. individual (No. 3 of 1st group) in quiet respiration ‡ Same individual with deep expiration. § Same individual with deep expiration.

1.1 cm, the average was 0.4 cm greater by teleroentgenogram.

3 Median left In all except one case the median left diameter was greater as obtained by teleroentgenogram, in that one case the ML by teleroentgenogram was 0.3 cm less than by orthodiagram. The average difference was 0.7 cm greater by teleroentgenogram.

4 Longitudinal The teleroentgenographic measurements of L were greater than the orthodiagraphic measurements in all cases, the greatest difference recorded by the two methods was 3.3 cm and the least was 0.3 cm. The teleroentgenographic measurements of L averaged 1.2 cm greater than the orthodiagraphic measurements.

5 Great vessels In the measurements of the great vessels the two methods gave the same results in one case, in one case the teleroentgenogram showed G V to be 0.2 cm less, in another case 0.3 cm less than shown by orthodiagram, and in seven cases this measurement was greater by teleroentgenogram, the greatest difference being 1.5 cm, the average difference in the ten cases was 0.4 cm greater by teleroentgenogram.

6 Thorax In all ten cases the teleroentgenographic intrathoracic diameters were greater, the greatest difference was 4.6 cm while the least difference was 1.6 cm. The average obtained by the teleroentgenogram was 2.8 cm greater than that of the orthodiagram.

7 Cardiothoracic ratio The results given are expressed as percentages of the transverse cardiac diameter as compared to the internal diameter of the

thorax. The teleroentgenogram showed a smaller percentage in eight cases, an equal percentage in one case, and a greater percentage in one case. The CTR by teleroentgenogram averaged 2.5 per cent less than that by orthodiagram.

8 Area In the enlarged hearts we found that the actual difference in areas as recorded in square centimeters was well-marked. The teleroentgenogram gave a larger area in every case. The greatest difference in the two methods was in a case in which the teleroentgenogram showed 46 sq cm more area than did the orthodiagram, in the case in which the least difference occurred the area by teleroentgenogram was 4 sq cm greater. The teleroentgenographic heart area averaged 25.4 sq cm greater than that by orthodiagram. Again expressing the results in percentages, we found the greatest difference in a case in which the teleroentgenographic area was 26.2 per cent greater than the orthodiagraphic area and in the case showing the least difference the teleroentgenographic area was 2.7 per cent greater. The teleroentgenographic area averaged 14.9 per cent greater than that by orthodiagram.

III SPECIAL CASES

A. Aortic Aneurysm of the Aorta

In this case (figure 3) the diameter of the heart and the aneurysmal sac furnish an interesting comparison. The orthodiagraphic measurements were as follows: (a) Diameter of aneurysm (frontal plane silhouette) 10.2 cm. (b) transverse diameter of heart 11.5 cm. (c) heart area 44 sq cm, aneurysmal area 81 sq cm. The teleroentgenographic measurements were

(a) Diameter of aneurysm, 10.8 cm ,
 (b) transverse diameter of heart, 12.9 cm ; (c) heart area, 113 sq cm ; (d) aneurysmal area, 88 sq cm The reader is referred to the table for more detailed measurements

B Pericarditis with Effusion and later Artificial Hydropneumopericardium

In this case it is interesting to compare (1) the diameter of the cardiac shadow before a pericardial paracentesis had been performed orthodiagraphic transverse diameter, 20.5 cm , teleroentgenographic transverse diameter, 24.5 cm * (2) the diameter of the pericardial sac after air had been injected orthodiagraphic transverse diameter, 18.6 cm , teleroentgenographic transverse diameter, 19.8 cm Then contrast the two groups of measure-

ments with (3) the true diameters of the heart observed during the state of artificial hydropneumopericardium, orthodiagraphic transverse diameter, 12.4 cm , teleroentgenographic transverse diameter, 13.6 cm

C Case showing Effect of Respiration

The detailed measurements in this case are presented in the table 3a shows the measurements obtained during normal quiet respiration, 3b shows those obtained during full inspiration (figure 4) , and, finally, 3c those show-

*This unusually large difference of 4 cm between the orthodiagraphic and teleroentgenographic transverse diameter measurements is due in part to the large diameter itself and in part to exaggeration resulting from a difference in the shape of the pericardial sac due to a somewhat lower position of the diaphragm in the case of the teleroentgenogram

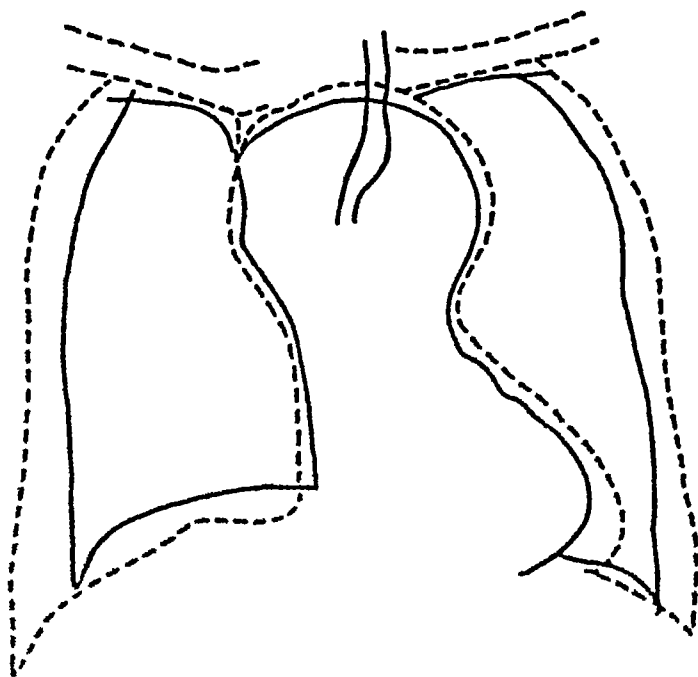


Figure 3. E.N.S. Group III, Case 1.

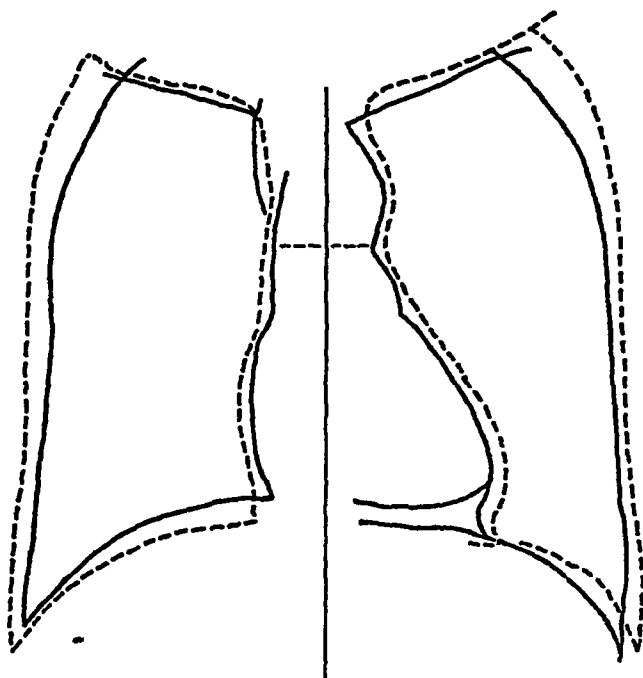


Figure 4. P.D.C. Group III Case 3.
(*Full Inspiration*)

FIG 4 Orthodiagram (solid line) and teleroentgenogram (dotted line) of P.D.C. Case 3 of Group III at the height of deep inspiration. Reduced to $\frac{1}{4}$ actual size. See table for measurements.

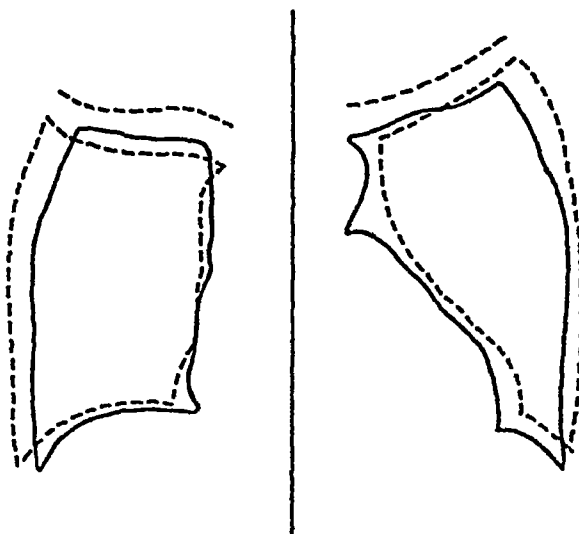


Figure 5 P.D.C. Group III Case 3.
(*Full Expiration*)

FIG 5 Orthodiagram (solid line) and teleroentgenogram (dotted line) of P.D.C. Case 3 of Group III at maximum full expiration. Reduced to $\frac{1}{4}$ actual size. See table for measurements.

ing the results of full expiration (figure 5). The measurements obtained during quiet normal breathing fit about halfway between the two extreme phases of respiration. The transverse heart diameters show a difference of 1.4 cm, 0.9 cm, and 1.3 cm in the respective phases of respiration (quiet breathing, full inspiration, and full expiration), as recorded by the two methods, the teleroentgenographic record being greater in each case. The intrathoracic diameter showed marked variations with respiration, the diameter by orthodiagram at full inspiration being 28.5 cm and during full expiration 25.0 cm, as compared with 29.0 cm and 27.0 cm respectively when recorded by the teleroentgenogram. The greatest variation in cardiothoracic percentages was shown by the orthodiagram as follows: full inspiration 40.3 per cent, full expiration, 59.0 per cent. The areas also showed marked changes according to the phase of respiration and the methods used, here again the orthodiagram showed the most marked difference between 88 sq. cm in inspiration and 112 sq. cm in expiration.

From this it seems that for cardiac measurements quiet breathing is preferable to either full inspiration or full expiration. It was very difficult for us to insure that we were obtaining readings exactly the same phase of deep respiration, especially at the extreme of expiration. Since the respiratory excursion was so small, the thoracic diameter was not increased by the use of the teleroentgenogram. The difference in the measurements of the thoracic diameter by the two methods was 0.5 cm. The difference in the measurements of the cardiothoracic ratio by the two methods was 1.7 per cent.

SUMMARY AND CONCLUSIONS

We have presented herewith, first, a brief note on the introduction of orthodiagraphic and teleroentgenographic methods for obtaining cardiac and thoracic measurements, and second, measurements with each of these methods in a series of twenty-two individuals, ten normal healthy persons and twelve with abnormalities of heart, aorta, or pericardium. The results may be briefly summarized as follows:

In each of the diameters measured the teleroentgenographic average was greater than the orthodiagraphic average, and, as would be expected, the thoracic measurements showed a greater difference than the cardiac measurements. The transverse diameter of the heart averaged about 1 centimeter greater by teleroentgenogram than by orthodiagram (with an extreme difference of 1.8 cm.). The cardiothoracic ratio (percentage) was essentially the same by orthodiagraphy and by teleroentgenography in both normal and abnormal groups, averaging only 17 per cent greater by orthodiagraphy in the combined series of 10 normal and 10 enlarged hearts (0.9 per cent greater in the first group and 2.5 per cent greater in the second group). The absolute and percentage differences in area showed the teleroentgenogram greater than the orthodiagram in all cases of both groups. The absolute difference in area in the group with normal hearts averaged 22.2 sq. cm. greater and in the group with the enlarged hearts 25.4 sq. cm. greater; the teleroentgenographic area was greater than the orthodiagraphic area in the normal group by 21.7 per cent and in the enlarged group by 14.9 per cent.

That the differences between the orthodiagraphic and teleroentgenographic measurements given here are not to be accounted for by simple variations in an individual's heart size and chest size at different times has been proved by two findings: first, the consistently greater measurements by the teleroentgenogram, and second, control measurements of the same cases by the same method on different days but under the same conditions.

We have included in this study measurements of an aortic aneurysm and of a distended pericardium respectively, and additional measurements of one of the normal cases to demonstrate the striking contrast between the effects of full inspiration and of full expiration on the cardiac and thoracic measurements.

We have found, as was to be expected, that the orthodiagraphic method gives smaller measurements of cardiac and thoracic diameters than does the teleroentgenographic method and that the larger the object studied the greater the error due to divergence when the teleroentgenogram (seven foot plate) is

used. Since the ratio of magnification is always the same, however, in the teleroentgenogram, we should theoretically find the cardiothoracic percentage equal by the two methods. In our series of cases there was found a very slight difference in the ratios by the two methods which may be said to fall within the error for the measurements themselves. The greater cardiac area measurement by teleroentgenogram is a uniform finding and averaged 15 to 25 per cent in our cases.

Thus, in giving roentgen measurements of cardiac and intrathoracic diameters and of cardiac area it is essential to state whether these measurements are made by orthodiagram or by teleroentgenogram. The difference between the results of the two methods is great enough to render direct comparison misleading, and it is of course not right for those using the teleroentgenographic measurements (such as are used widely in the United States) to check such measurements against those recorded in tables based on orthodiagraphy (such as are standard throughout Europe).

BIBLIOGRAPHY

- DIETLEN, H. *Wien klin Rundschau*, 1905 xix, 355. Quoted from Dietlen, H. *Orthodiagraphie und Teleroentgenographie als Methoden der Herzmessung*. Munch med Wchnschr, 1913, ix, 1763.
- GOCHT, H. *Handbuch der Röntgenlehre* 1898. Quoted from Köhler, A. *Teleroentgenographie des Herzens*, Deutsch med Wchnschr 1918 xxxv, 186.
- GRODFEL, F. M. *Die Röntgendiagnostik der Herz- und Gefässerkrankungen*. Verlag von Hermann Meusser, Berlin 1912.
- KÖHLER, A. *Teleroentgenographie des Herzens*. Deutsch med Wchnschr 1918 xxxv, 186.
- MORITZ, F. *Line Methode um beim Röntgenverfahren aus dem Schattenbild eines Gegenstandes dessen wahre Größe zu ermitteln (Orthodiagraphie) und die exakte Bestimmung der Herzgröße in diesem Verfahren*. M. med Wchnschr 1911 xlviii, 922.
- ROSENFIELD, G. *Die Diagnostik der Herzkrankheiten*. J. F. Bergmann's Verlag, Wiesbaden 1921, p. 127.
- VAN ZWOLLEN, J. G. *Lehrbuch der Crane*. (Quoted March 28, 1919). Published in *Lehrbuch der Crane*. Rotterdam 1922, p. 32.

A New Percussion Technic

By FRANK SMITHIES, Sc D , M D , M A C P , *Chicago, Illinois*

DURING the World War, when a member of a "draft-board team", the writer was, of necessity, compelled to examine physically a great number of candidates over a period of many months. In percussing thoraces, particularly by the ordinary mid-finger of one hand (hammer) to mid-finger of the other hand (pleximeter) method, a few hours' work resulted in a very sore dorsal surface of the pleximeter finger, even when the nail on the "hammer finger" was kept short, shaped broadly and smoothed by means of the emery stick. The joint of the hammer finger not rarely became swollen and painful and the extensor muscles and wrist of that hand ached long after the examining session. Muscle cramp resulting from over-use, caused work to be difficult and at times inaccurate.

As a consequence of experience gained in this work upon prospective soldiers and later in the handling of considerable material when teaching medical students a method of percussion, a radically different from that commonly known and practiced, was developed. This method proved of such advantage that it has no equal in the history of percussion. In later years, when the writer, as a member of the medical staff of the United States Army, was called upon to examine recruits, the new method was found to be of great

advantages over the commonly employed percussion technic.

In brief, the percussion technic employed is as follows:

The pleximeter finger (or fingers) is placed upon the thorax or whatever body section is to be percussed, in the usual manner. The pleximeter finger (or fingers) is pressed firmly or lightly upon the body wall, accordingly as superficial or deep percussion is desired (Figure 1). The striking "hammer" is arranged by crossing the flexor surface of that portion of the second finger beyond the last interphalangeal joint of the percussing hand over the extensor surface of the index finger of the same hand, so as to have it cover practically the whole nail surface and that part of the index finger distal to the last interphalangeal joint. Then, by a quick, snapping movement, the second finger is slid from the index finger so as to strike forcibly the extensor surface of the "pleximeter" finger (or fingers) of the other hand (Figure 2). A little practice in so snapping apart the index and second fingers of the "hammer" hand, readily enables one to strike a considerable "sawtooth" and rounding stroke upon the pleximeter. Accordingly as the "hammer" finger are snapped apart, the varying degree of interphalangeal joint flexion or extension, the stroke is quick or slow, heavy or light, and the pleximeter

The smooth surface of the finger nail of the index finger allows very free "snapping" and results in blows which evoke fine, resonant notes. Particularly well do such tones serve when patients are being examined before a considerable group.

In carrying out this percussion technic, body surfaces — chest, etc. — are covered just as they are when using finger-tip (hammer) to extensor surface of second finger of other hand. All parts may be reached readily. In percussing lung apices, sometimes individual structural peculiarities of subjects make it desirable to strike the thumb instead of the second finger. When the fingers of the "pleximeter hand" are separated (e.g., a finger placed in each intercostal space) a large area may be percussed rapidly, and, as is often highly desirable, comparisons

and contrasts between the percussion tones are possible quickly, without moving the "pleximeter" about and while so doing, running the risk of losing previously elicited tones. This maneuver is employed very advantageously during chest percussion when it is desired to locate the borders of consolidation, fluid, atypical air collections, etc.

After dexterity and accuracy have been achieved by a few weeks practice with the method and when the fingers have lost their memories of the present, commonly-used percussion technic many interesting and useful variations in the application of the method described will suggest themselves.

Some of the advantages of the percussion technic here mentioned appear to be

- 1 Long continued work with avoid-



FIG. 1. Position of hands and fingers at beginning of percussion. A, "pleximeter" hand; B, "hammer" hand, with second finger crossed over first finger to "snap" to deliver percussion stroke to pleximeter.

ance of fingers made painful by trauma and cramp

2 The avoidance of unsightly, close-cut nails on "hammer" fingers

3. A clearer percussion tone and the ease with which such may be modified in volume and amplitude.

4 Rapid comparisons or contrasts

in percussion tones in the several sections of a part being examined—e.g., the thorax

5 When teaching or demonstrating in class work, the quick and easy demonstration of percussion anomalies

6 When the method has been mastered, greater percussion accuracy

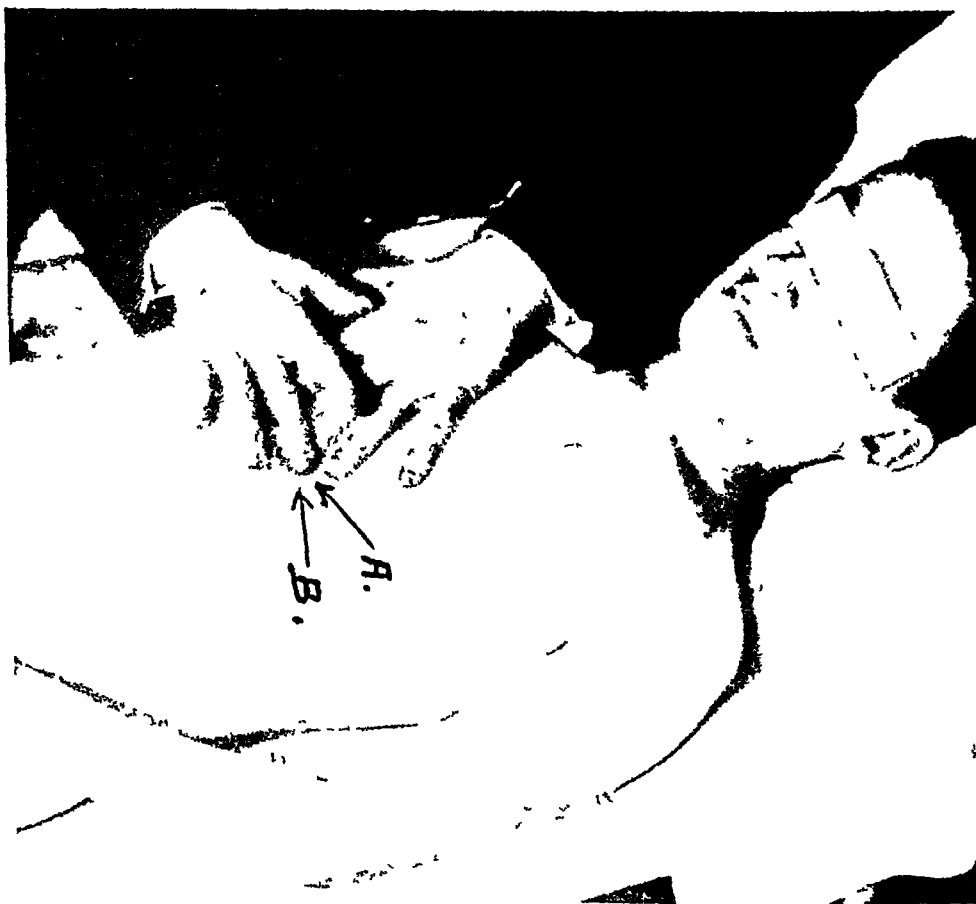


FIG 2 Position of hands after percussion stroke is delivered A, pleximeter finger, and B, second finger of "hammer" hand at contact with second finger of pleximeter hand

Further Observations on Primary Carcinoma of the Liver in Chinese

By G F STRONG, M D, and H H PITTS, M D, *Vancouver, B C*

IN a previous article¹ in 1930 we reported nine cases of primary carcinoma of the liver seen at the Vancouver General Hospital between 1920 to 1927, inclusive. Eight of these were Chinese and one a white man. We now add three additional cases seen in the four years, 1928 to 1931, of which two are Chinese and one white. This total of twelve cases of undoubted primary carcinoma of the liver in the twelve year period is large, and is an indication of the extreme frequency of this type of malignancy among these Chinese. Analysis of the incidence in the separated racial groups will show that as far as whites are concerned our findings are comparable to those reported elsewhere. When the incidence in Chinese is considered it is found to be very high, so high that it would seem wise to consider the matter further to ascertain if possible what factors account for this great frequency.

Primary carcinoma of the liver is one of the rarer forms of cancer. Counsellor and McIndoe² collected a series of 42,276 autopsies in which the incidence of this malignancy was only 0.14 per cent. The incidence in our series was 12 cases in 1967 autopsies or

0.61 per cent. This is so extremely high that it immediately raises the question as to the criteria used for making this diagnosis. It should be mentioned that during these twelve years we have seen other cases so diagnosed which have been rejected because the proof seemed inadequate. We have included only those cases in which a complete autopsy was performed and in which, furthermore, the microscopic sections showed a definite primary carcinoma of the liver of either the hepatoma or cholangioma type. An additional criterion was the presence of a definite cirrhosis. This was true in all but one of our cases as will be described in detail later. To further satisfy ourselves we submitted most of this material to Dr Wm Boyd, Professor of Pathology at the University of Manitoba, who was kind enough to review it and to have made the photomicrographs which illustrate this paper. We feel that there can be no doubt as to the diagnosis of these selected cases.

When the percentage incidence in the different racial groups is considered (table I), the enormous increased frequency in the Chinese is immediately evident. Among whites there were 2 cases in 1828 autopsies or 0.109 per cent, which is slightly more than the incidence in the Chinese.

¹Presented at the San Francisco meeting of the American College of Physicians April 5, 1932.

TABLE I

Incidence of Primary Carcinoma Liver	NUMBER OF CASES	NUMBER OF AUTOPSIES	PERCENTAGE INCIDENCE
Total	12	1967	0.61
White	2	1828	0.109
Chinese	10	139	7.19
Counsellor and McIndoe ²		42276	0.14

incidence in Chinese with 10 cases in 139 autopsies, or 7.19 per cent, is extremely high

The Chinese resident in British Columbia come almost entirely from the province of Kwangtung in the south of China, most of them being Cantonese. In trying to discover what factors might be responsible for this tremendous incidence of primary carcinoma of the liver we had to secure what information we could from that part of China. Statistics from Central or Northern China are of little, if any, assistance because of the great difference in environmental factors. It is impossible to obtain accurate autopsy statistics from Kwangtung, but we were able to secure some information of value. Most of this was reported in our previous paper and needs only brief mention here. There can be no doubt that the incidence of chronic diseases of the liver, both cirrhosis and cancer, is greatly increased in Southern Asia and particularly in the south of China. One autopsy series showed more primary carcinoma of the liver than primary carcinoma of the stomach. It is also generally agreed that one, if not the main, cause for this increased incidence of chronic liver disease is the very great frequency of chronic intestinal disease including infestation with intestinal parasites. The commonest and probably most likely cause of chronic liver disease is the liver fluke,

Clonorchis sinensis, which is acquired by eating raw fish, a habit very common in this part of China. There are certain areas in Southern China where infestation with this liver fluke is so general as to approximate 100 per cent of the population. In such areas the incidence of primary carcinoma of the liver is known to be high. All of our Chinese cases showed a definite cirrhosis which we take to indicate that the liver had been subjected to long continued chronic irritation before the development of the malignant process. The pathogenesis would appear to be early and repeated, or long continued, infection with liver fluke with resulting chronic irritation leading to the development of a low grade hepatitis and cirrhosis. After years of this irritation some cases develop malignant degeneration. The nature of the irritant and whether mechanical or toxic or both is not clear. This is, however, another instance of the potency of chronic irritation in the production of cancer.

It is not to be inferred that all liver disease results from *Clonorchis* infection, for other parasites also occur and chronic bacterial infections of the intestinal tract are not unusual. The liver fluke is certainly the most common offender. Investigation has shown that the great majority (75 per cent in one series) of Chinese coming to British Columbia are infested with liver flukes. Ordinarily such infestation causes no symptoms and is not considered a cause for exclusion from the country.

Because of the growth of Vancouver and the failure of hospital facilities to keep pace with that growth, the number of Chinese patients admitted to the Vancouver General Hospital is gradu-

ally being reduced. Overcrowding of that institution, particularly during 1927-1930, has led to the gradual exclusion of the Chinese patient. A separate hospital for Orientals has also decreased the number of Chinese admitted to the General Hospital. Reference to table II shows the reduction in the

currence. It is regretted that the clinical details in some of these cases are so meager. In some instances the patient was moribund on admission and no history was obtainable. The last case is reported in more detail because it was one of the two in which the correct ante mortem diagnosis was made.

TABLE II
Comparison of Deaths and Autopsies Among Whites and Chinese

YEAR	TOTAL DEATHS	WHITE DEATHS	AUTOPSIES WHITE		CHINESE DEATHS	AUTOPSIES CHINESE	
			No	%		No	%
1920	688	641	113	17.6	47	19	40.4
1921	598	568	121	21.3	30	12	40.0
1922	654	598	126	21.0	56	19	33.9
1923	552	513	124	24.1	39	10	25.6
1924	557	508	78	15.3	49	17	34.6
1925	663	616	95	15.4	47	13	27.6
1926	689	641	133	20.7	48	16	33.3
1927	738	714	119	16.6	24	9	37.5
	5139	4799	909	19	340	115	34.1
1928	906	877	175	19.9	29	4	13.8
1929	900	871	187	21.4	29	8	27.6
1930	840	816	219	26.8	24	5	20.8
1931	796	771	338	43.8	25	7	28.0
	3442	3335	919	27.5	107	24	22.5
	8581	8134	1828	21.9	447	159	30.2
			139				
Total Autopsies —			1967				

number of deaths and autopsies on Chinese. If this continues, as seems most likely, we will shortly see only an occasional Chinese at the Vancouver General Hospital. Table II shows also the increasing percentage of autopsies on whites. It is of interest that practically the same number of autopsies on whites was performed in the four year period, 1928-1931, as in the previous eight years and in each series there occurred one case of primary carcinoma of the liver in a white man.

The cases are reported briefly here-with in the order in which they appeared in our original article with the three recent cases in order of their oc-

ABSTRACT OF CASES

Case I. Q. S. hospital no. B76010 Chinese laborer, aged 45, was admitted Oct. 22, 1926 complaining of swelling of the abdomen and legs and progressive weakness. He had been in Canada 20 years. In January, 1926 he became weak and unable to work. In July his abdomen was larger and a tender lump appeared in right epigastrium. He lost 11 to 18 lbs. in weight.

Examination showed an emaciated, middle-aged Chinese with distention of the right chest. His abdomen was tender with fluid. After 210 cc. of ascitic fluid had been removed, the tender nodule passed and he felt better. The liver was palpable in the epigastrium and right hypochondrium. The liver specimen was 100 gms. with irregular surface.

tion. The spleen was not enlarged. There was considerable edema of legs and feet.

Laboratory observations Wassermann (blood), negative. Urine albumen, a trace, and occasional hyaline casts. N.P.N. 33 mgm. per 100 c.c. of blood. Red blood cells, 3,602,000, hemoglobin, 70%, white blood cells, 5,500. Gastro-intestinal x-ray, negative. Fluoroscopic examination showed the right side of diaphragm to be elevated to the level of the second rib, apparently due to an enlarged liver. Because of our previous observations of primary carcinoma of the liver in Chinese such a diagnosis was made in this case. He remained in hospital four months, until his death, Feb 13, 1927. The clinical course was that of a rapidly progressive hepatic cirrhosis.

Autopsy report. The body was that of an emaciated, middle aged Chinese, with abdomen distended with fluid. The right lung was firm in its lower half and seemed to be contiguous with the liver. The reason for this compression was seen to be due to an extremely large growth originating in the liver which had grown through the diaphragm on the right and produced an upward displacement of the lower lobe of lung but had not invaded the lung proper. On section it presented a somewhat lobulated grayish-white, firm, slightly bile-tinged, carcinomatous appearance. The right lobe of the liver was generally involved, the left less so. The portal system was markedly compressed and the gastro-intestinal tract intact throughout. The left lung was negative. The heart was removed without detaching it from the right lung, and a projection of the growth the size of a hen's egg was found in the right auricle. The peritoneal cavity was filled with chylous ascitic fluid. Further examination of the body revealed no other primary focus or other pathology. An anatomical diagnosis of primary carcinoma of the liver with extension through the right side of the diaphragm to the right pleural cavity and right auricle was made. Histological examination of the various sections from the liver confirmed this and showed an associated extensive cirrhosis.

Diagnosis. Primary carcinoma of liver (cholangioma type), with cirrhosis.

Case II. J. Y., hospital no A95277, Chinese laborer, aged 33, was admitted June 18, 1920. No history was obtainable. He presented marked edema of the feet, legs and abdomen. The liver was enlarged and nodular. The patient lived only one and one-half hours after admission.

Autopsy report. There was edema of the lower extremities. The peritoneal cavity showed ascities. The liver weighed 6,650 gm. There were grayish-white nodules of varying size, from 1 to 6 cm in diameter, almost all in the right lobe. The intervening liver tissue was grossly cirrhotic. Metastatic nodules were present in both lungs. No evidence of other primary growth was revealed on further examination.

Microscopic observations. In this tumor the cells were not as large as those seen in several of the other tumors of this series. They were slightly pleomorphic, and the nuclei were hyperchromatic, pyknotic and mitotic. The cells were arranged in solid, relatively small, aggregations with no attempt at acinar or duct formation, and in one area a definite tumor embolus was seen in a large vein. A well defined cirrhosis was present throughout.

Diagnosis. Primary carcinoma of the liver (hepatoma type), with cirrhosis.

Case III. Y. M., a Chinese laborer, aged 45, was admitted to the hospital on March 11, 1921. The past history revealed nothing significant. For fourteen months he had suffered from loss of weight and pain in the upper part of the abdomen, with occasional attacks of fever. The patient was emaciated, with definite ascites and edema of the feet and legs. The liver was enlarged. He died on April 4.

Autopsy report. There was marked edema of the lower extremities and cavity was filled with bloody fluid. The liver weighed 4,970 gm, with the right lobe almost completely replaced by large, grayish-white tumor masses, one, superficially placed, being extremely degenerated and hemorrhagic, apparently the source of the intraperitoneal hemorrhage. The left lobe also was studded with smaller nodules, many of which were bile stained, the intervening liver substance being cirrhotic. Metastatic nodules were

found in the lungs, omentum and brain. No other primary growth was found on further examination of the body.

Microscopic observations Sections through the tumor tissue showed it to consist of an aggregation of large, atypical, pleomorphic, hyperchromatic cells, many of which were extremely large with multinucleation and mitoses. In some areas the cells were arranged in fairly compact masses, in others more loosely arranged, but on the whole the stroma was sparse and fairly general degeneration was apparent throughout. Definite periportal cirrhosis was in evidence.

Diagnosis Primary carcinoma of the liver (hepatoma type), with cirrhosis.

Case IV G Y, hospital no B2907, Chinese laborer, aged 57, was admitted Jan 17, 1921. He presented swelling of the feet and abdomen, weakness and loss of weight for one month. Ascites and edema of the feet were present. He died on Jan 24.

Autopsy report Relatively little of note was found on external examination. There was no edema of the extremities or ascites. The peritoneal cavity was filled with clotted and fluid blood. The omentum was adherent apparently by recent adhesions to a mass in the inferior aspect of the right lobe of the liver in which a deep hemorrhagic split was present, evidently the source of the hemorrhage. The liver weighed 3,060 gm. It had been converted into a rather sclerotic, yellowish-white mass with relatively little normal liver tissue present, with areas of necrosis throughout. Finger-like processes of tumor tissue were found protruding into the inferior vena cava. No metastases were found in the lungs, and there was no evidence of other primary growth elsewhere in the body.

Microscopic observations The cells were large, fairly uniform, hyperchromatic and atypical, the nuclear material was especially dense but the cells generally showed none of the giant-like forms seen in many of the hepatoma types. They were arranged about definite, variously sized, ductlike spaces while in many areas definite tumor emboli were seen within vascular channels. Degenerative and inflammatory changes were in evidence with a definite but relatively fine cirrhosis throughout.

Diagnosis Primary carcinoma of the liver (cholangioma type), with cirrhosis.

Case V L H K, hospital no B21104, Chinese laborer, aged 47, was admitted June 24, 1922. No history was obtainable. He complained of ascites and edema of the legs. He died on June 25.

Autopsy report There was some edema of the lower extremities. The peritoneal cavity was filled with serosanguineous fluid. The liver weighed 2,400 gm and was markedly cirrhotic in appearance, with many smaller and larger grayish-white nodules scattered throughout, chiefly in the right lobe. In one area, a process of tumor tissue protruded into the right portal vein. Several grossly involved perigastric lymph glands were present. There was no evidence of further metastases or other primary growth on further examination.

Microscopic observations The cells were pleomorphic, generally pale staining and arranged in solid sheets surrounding spaces which were evidently vascular sinuses lined by elongated endothelial cells, apparently of the Kupffer type. In other areas, aggregations of dissimilar cells were seen which were of relatively enormous size, pale and with multinucleation into many bizarre formations. Dense fibrotic bands surrounded these areas while in the former areas definite but finer cirrhosis was evident.

Diagnosis Primary carcinoma of the liver (hepatoma type), with cirrhosis.

Case VI H C, hospital no B25404, Chinese laborer, aged 21, was admitted Nov 5, 1922. Six days before admission he noted anorexia, headache and increasing vomiting. He was in coma at the time of admission and died two days later. Ascites was present at the time of death. The liver was palpable. There was no edema of the feet.

Autopsy report There was no edema or ascites. The liver weighed 1,950 gm. A single, large, grayish white mass almost completely replaced the right lobe of the liver with a few smaller discrete nodules surrounding it. No metastases were seen on further examination of the body.

Microscopic observations The cells were uniform, large, rather small, and the

tion. The spleen was not enlarged. There was considerable edema of legs and feet.

Laboratory observations. Wassermann (blood), negative. Urine albumen, a trace, and occasional hyaline casts. N.P.N. 33 mgm. per 100 c.c. of blood. Red blood cells, 3,602,000, hemoglobin, 70%, white blood cells, 5,500. Gastro-intestinal x-ray, negative. Fluoroscopic examination showed the right side of diaphragm to be elevated to the level of the second rib, apparently due to an enlarged liver. Because of our previous observations of primary carcinoma of the liver in Chinese such a diagnosis was made in this case. He remained in hospital four months, until his death, Feb. 13, 1927. The clinical course was that of a rapidly progressive hepatic cirrhosis.

Autopsy report. The body was that of an emaciated, middle aged Chinese, with abdomen distended with fluid. The right lung was firm in its lower half and seemed to be contiguous with the liver. The reason for this compression was seen to be due to an extremely large growth originating in the liver which had grown through the diaphragm on the right and produced an upward displacement of the lower lobe of lung but had not invaded the lung proper. On section it presented a somewhat lobulated grayish-white, firm, slightly bile-tinged, carcinomatous appearance. The right lobe of the liver was generally involved, the left less so. The portal system was markedly compressed and the gastro-intestinal tract intact throughout. The left lung was negative. The heart was removed without detaching it from the right lung, and a projection of the growth the size of a hen's egg was found in the right auricle. The peritoneal cavity was filled with chylous ascitic fluid. Further examination of the body revealed no other primary focus or other pathology. An anatomical diagnosis of primary carcinoma of the liver with extension through the right side of the diaphragm to the right pleural cavity and right auricle was made. Histological examination of the various sections from the liver confirmed this and showed an associated extensive cirrhosis.

Diagnosis. Primary carcinoma of liver (cholangioma type), with cirrhosis.

Case II. J. Y., hospital no. A95277, Chinese laborer, aged 33, was admitted June 18, 1920. No history was obtainable. He presented marked edema of the feet, legs and abdomen. The liver was enlarged and nodular. The patient lived only one and one-half hours after admission.

Autopsy report. There was edema of the lower extremities. The peritoneal cavity showed ascities. The liver weighed 6,650 gm. There were grayish-white nodules of varying size, from 1 to 6 cm. in diameter, almost all in the right lobe. The intervening liver tissue was grossly cirrhotic. Metastatic nodules were present in both lungs. No evidence of other primary growth was revealed on further examination.

Microscopic observations. In this tumor the cells were not as large as those seen in several of the other tumors of this series. They were slightly pleomorphic, and the nuclei were hyperchromatic, pyknotic and mitotic. The cells were arranged in solid, relatively small, aggregations with no attempt at acinar or duct formation, and in one area a definite tumor embolus was seen in a large vein. A well defined cirrhosis was present throughout.

Diagnosis. Primary carcinoma of the liver (hepatoma type), with cirrhosis.

Case III. Y. M., a Chinese laborer, aged 45, was admitted to the hospital on March 11, 1921. The past history revealed nothing significant. For fourteen months he had suffered from loss of weight and pain in the upper part of the abdomen, with occasional attacks of fever. The patient was emaciated, with definite ascites and edema of the feet and legs. The liver was enlarged. He died on April 4.

Autopsy report. There was marked edema of the lower extremities and cavity was filled with bloody fluid. The liver weighed 4,970 gm., with the right lobe almost completely replaced by large, grayish-white tumor masses, one, superficially placed, being extremely degenerated and hemorrhagic, apparently the source of the intraperitoneal hemorrhage. The left lobe also was studded with smaller nodules, many of which were bile stained, the intervening liver substance being cirrhotic. Metastatic nodules were

found in the lungs, omentum and brain. No other primary growth was found on further examination of the body.

Microscopic observations Sections through the tumor tissue showed it to consist of an aggregation of large, atypical, pleomorphic, hyperchromatic cells, many of which were extremely large with multinucleation and mitoses. In some areas the cells were arranged in fairly compact masses, in others more loosely arranged, but on the whole the stroma was sparse and fairly general degeneration was apparent throughout. Definite periportal cirrhosis was in evidence.

Diagnosis Primary carcinoma of the liver (hepatoma type), with cirrhosis.

Case IV G Y, hospital no B2907, Chinese laborer, aged 57, was admitted Jan 17, 1921. He presented swelling of the feet and abdomen, weakness and loss of weight for one month. Ascites and edema of the feet were present. He died on Jan 24.

Autopsy report Relatively little of note was found on external examination. There was no edema of the extremities or ascites. The peritoneal cavity was filled with clotted and fluid blood. The omentum was adherent apparently by recent adhesions to a mass in the inferior aspect of the right lobe of the liver in which a deep hemorrhagic split was present, evidently the source of the hemorrhage. The liver weighed 3,060 gm. It had been converted into a rather sclerotic, yellowish-white mass with relatively little normal liver tissue present, with areas of necrosis throughout. Finger-like processes of tumor tissue were found protruding into the inferior vena cava. No metastases were found in the lungs, and there was no evidence of other primary growth elsewhere in the body.

Microscopic observations The cells were large, fairly uniform, hyperchromatic and atypical, the nuclear material was especially dense but the cells generally showed none of the giant-like forms seen in many of the hepatoma types. They were arranged about definite, variously sized, ductlike spaces while in many areas definite tumor emboli were seen within vascular channels. Degenerative and inflammatory changes were in evidence with a definite but relatively fine cirrhosis throughout.

Diagnosis Primary carcinoma of the liver (cholangioma type), with cirrhosis.

Case V L H K, hospital no B21104, Chinese laborer, aged 47, was admitted June 24, 1922. No history was obtainable. He complained of ascites and edema of the legs. He died on June 25.

Autopsy report There was some edema of the lower extremities. The peritoneal cavity was filled with serosanguineous fluid. The liver weighed 2,400 gm and was markedly cirrhotic in appearance, with many smaller and larger grayish-white nodules scattered throughout, chiefly in the right lobe. In one area, a process of tumor tissue protruded into the right portal vein. Several grossly involved perigastric lymph glands were present. There was no evidence of further metastases or other primary growth on further examination.

Microscopic observations The cells were pleomorphic, generally pale staining and arranged in solid sheets surrounding spaces which were evidently vascular sinuses lined by elongated endothelial cells, apparently of the Kupffer type. In other areas, aggregations of dissimilar cells were seen which were of relatively enormous size, pale and with multinucleation into many bizarre formations. Dense fibrotic bands surrounded these areas while in the former areas definite but finer cirrhosis was evident.

Diagnosis Primary carcinoma of the liver (hepatoma type), with cirrhosis.

Case VI H C, hospital no B25496, a Chinese laborer, aged 21, was admitted Nov 5, 1922. Six days before admission he noted anorexia, headache and increasing vomiting. He was in coma at the time of admission and died two days later. Ascites was present, the liver was palpable. There was no edema of the feet.

Autopsy report There was no edema or ascites. The liver weighed 1,950 gm. A single, large, grayish-white mass almost completely replaced the right lobe of the liver with a few smaller discrete nodules surrounding it. No metastases were found and no other primary growth was revealed on further examination of the body.

Microscopic observations The tumor cells were uniform in size, rather small and for



FIG 1 (Case VI) Section of tumor, X 125 Well marked but aborted attempts at bile-duct formation are seen, the lining cells are very atypical and hyperchromatic, while frequent intercommunications between neighboring ducts are apparent

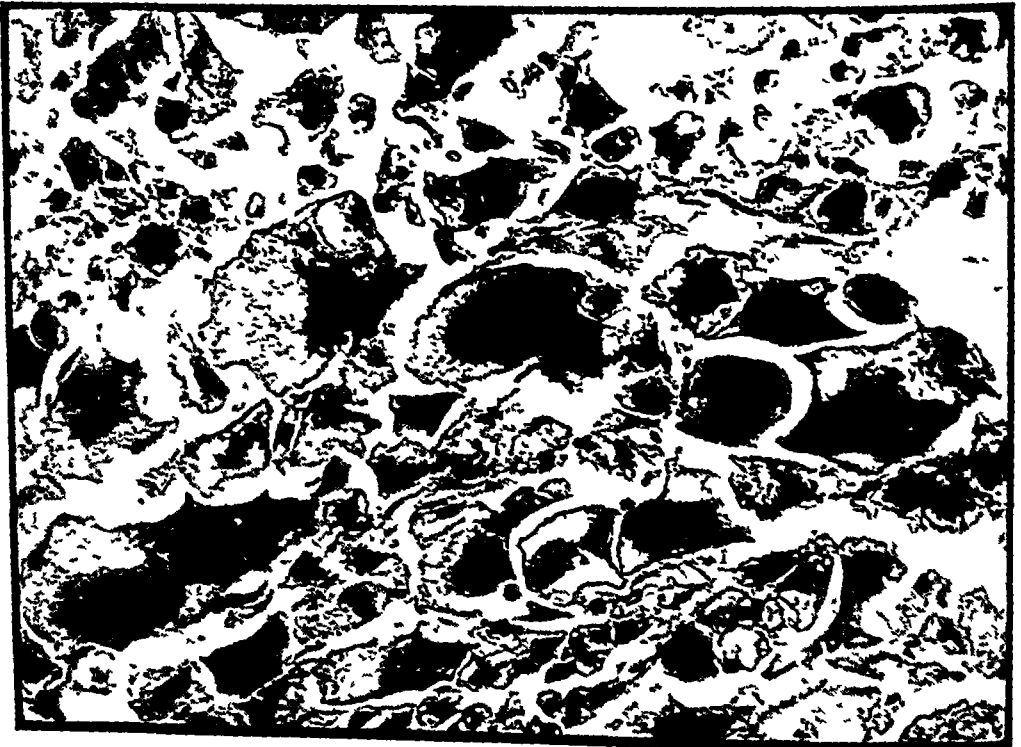


FIG 2 (Case III) Section of tumor, X 200 Numerous giant cell formations which are frequent chiefly in the hepatoma type of carcinoma of the liver

the most part surrounded gland or ductlike spaces, many of which were very elongated. Mitotic figures were numerous, but none of the very large cells were seen. A moderate amount of coarse cirrhosis was present throughout.

Diagnosis Primary carcinoma of the liver (cholangioma type), with cirrhosis.

Case VII L. L. F., hospital no. B31984, Chinese laborer, aged 53, was admitted May 15, 1923. Extreme emaciation was evident. There was no edema of the extremities. The liver was slightly enlarged. There was no ascites. The patient died on May 26.

Autopsy report External examination gave negative results. There was no ascites or edema. The liver weighed 2,000 gm and was studded with grayish-white nodules from 2 mm to 2 cm in diameter throughout both lobes. A few smaller, similar nodules were present in the spleen. Several metastatic nodules were found in three of the left ribs. No other primary growth was found on examination of the remainder of the body.

Microscopic observations Throughout these sections many cords and columns of pleomorphic cells of liver type were seen. Many of them were extremely large, with correspondingly large nuclei in which mitotic figures were frequent. Interspersed throughout were well defined bands of fibrous tissue of cirrhotic type in which fairly numerous but well developed biliary ducts were present.

Diagnosis Primary carcinoma of the liver (hepatoma type), with cirrhosis.

Case VIII McM., hospital no. B73930, a white laborer, aged 76 years, was admitted July 12, 1926. He had had weakness for two years. Edema of the feet, legs and abdomen was getting gradually worse. He was comatose at the time of admission and died on July 13.

Autopsy report There was edema of the lower extremities. Serosanguineous fluid was present in the peritoneal cavity and in both pleural cavities. The liver weighed 2,500 gm and was studded throughout with many grayish-white, bile stained nodules, while a larger superficial mass on the superior surface of the right lobe was adherent to the hepatic flexure of the colon but did not

extend into the lumen. Metastatic nodules were also present in the lungs. No other primary growth was found on further examination of the body.

Microscopic observations The picture presented in the sections from this tumor was practically identical with that seen in case VII, with the exception of an almost complete absence of cirrhotic changes. This would seem to be of interest owing to the fact that it is from one of the two white men in our series and is the only patient showing *no cirrhosis*.

Diagnosis Primary carcinoma of the liver (hepatoma type).

Case IX L. L., no hospital number, a Chinese laborer, aged 35, admitted to the emergency ward in an unconscious state on Sept. 5, 1927, and died within a few minutes after admission.

Autopsy record The body was that of a well-developed and nourished Chinese man. Nothing remarkable was apparent on external examination. The peritoneal cavity was completely filled with clotted and fluid blood, the source of which was found at the margin of the lower portion of the right lobe of the liver where a large degenerated carcinomatous mass, 8 by 6 cm., had eroded a large blood vessel, the thrombosed end of which was apparent. The liver was small, weighing only 1,090 gm. It was markedly cirrhotic. In the right lobe many grayish-white nodules, varying in size from that of a filbert to that previously noted, were seen, all more or less degenerated in appearance. The left lobe was free from nodules. A large tumor embolus was present in the first portion of the inferior vena cava. No gross metastases were found, and further examination of the body revealed no other primary growth.

Microscopic observations Sections through the liver showed the presence of many aggregations of atypical liver cells, some of which appeared to be from eight to ten times the size of the normal cells, irregular in shape, with large, single or multiple hyperchromatic nuclei frequently showing mitosis. No attempt at acinar or duct formation was apparent although in a few areas the cells were arranged in solid cylindric forma-

tions frequently showing considerable central degeneration. Extensive cirrhosis was present throughout with dense bands of fibrous tissue surrounding masses of these atypical cells. No tumor emboli were evident in the sections.

Diagnosis. Primary carcinoma of the liver (hepatoma type), with cirrhosis.

Case X S. H., coroner's autopsy, no history available. The body was that of a Chinese laborer, aged about 45, who had died Dec 16, 1928. Autopsy showed hemorrhage into the gastro-intestinal tract. No evidence of cancer of stomach or intestines was found. The liver showed extensive cirrhosis and carcinomatous nodules. Histologically, these were carcinoma of the hepatoma type. An extensive cirrhosis was present.

Diagnosis. Primary carcinoma of liver (hepatoma type), with cirrhosis.

Case XI S. G. P., hospital no C37523, a Chinese laborer, aged 44, was admitted Sept 14, 1930, and died Sept 26, 1930. His illness began one month previous to admission with indefinite pain in the right upper quadrant, sometimes followed by vomiting. Loss of weight (exact amount unknown), loss of appetite, acholic stools and icteroid tinge to conjunctivae were noted. Urine had been dark.

Physical examination. The patient was very emaciated, deeply jaundiced. The abdomen was not distended but tender over the right side. There was a nodular tender enlargement of the liver to below the level of umbilicus. X-ray examination of the gastro-intestinal tract was negative, and the Wassermann reaction was negative.

Autopsy report. The body was markedly jaundiced, emaciated, abdomen distended, right lower extremity edematous. There was a nodular mass in the right hypochondrium. Old fibrous pleurisy, bilateral, with an old tuberculous focus in apex of left upper lobe was found. There were 1½ pints of serosanguinous fluid in the abdominal cavity. The liver weighed 3,860 grms and was markedly nodular and greenish-yellow in color. On section, four large degenerated masses, varying from a navel orange to a medium sized grapefruit were seen, chiefly in the left lobe. Scattered throughout the re-

maining liver tissue were innumerable nodules varying from a bean to a walnut in size. These larger masses had varied colors: some cream-colored, others more deeply yellow and still others showing very extensive hemorrhagic extravasation. An advanced degree of cirrhosis was present in the intervening liver tissue. No evidence of any other neoplastic process was found and no metastases. A diagnosis of primary carcinoma of the liver was made. Histologically this proved to be of the hepatoma type and there was extensive cirrhosis.

Diagnosis. Primary carcinoma of liver (hepatoma type), with cirrhosis.

Case XII W. J., hospital no C44523, English gardener, aged 57, was admitted March 11, 1931, and died May 4, 1931.

Complaints. Patient had not been as well as usual, with drenching night sweats. There were many bad teeth which he wished extracted.

History. This man was born in England in 1874, lived from 1892 to 1911 in India, came to Canada in the latter part of 1911, was in the Great War for four and a half years, discharged, A-1, no pension. Patient states that he has never been in bed until last year, when he was admitted because of carbuncle on his back. This was incised and patient got along very well. While in India the patient had malaria on several occasions which cleared up with the administration of quinine. He had also had some dysentery. He was treated early and with satisfactory results. Patient had a Neisserian infection while living in India but denied lues.

Present illness. This patient reported about one week ago requesting that he have complete extraction of all his infected teeth. Prior to having this done a general examination was made and on questioning he stated that for the past three weeks he had been having very drenching night sweats and has had to change as often as ten times a night. About Christmas time he had a sharp pain in his right abdomen which doubled him up and at that time he reported to the Emergency Ward and was given some Sippy powders and placed on modified Sippy diet. He states that the pain cleared up shortly and he has not been bothered since. Bowels are

regular when at his work which gives him considerable exercise, but when lying in bed he requires aperients each night

Examination The patient was found to be a rather short man, slightly stooped and in poor physical condition. His weight has dropped 20 lbs in the last month. Teeth were in very bad shape, x-ray showed several infected roots. On the left side of neck at the angle of jaw there was a small hard gland, also a few very small glands in the posterior triangle, possibly from the infected teeth. Lungs and heart were normal. Blood pressure was 135/78. A tumor could be seen about midway between the costal margin and the pubes which moved freely on respiration and on palpation there could be felt a very definite, firm mass. This appeared to be the lower margin of the liver. Spleen was also palpable. Rectal examination was negative. Pupils and reflexes were normal.

Laboratory findings Gastro-intestinal x-ray examination showed no evidence of an intrinsic organic lesion. However, the hepatic flexure, ascending colon and proximal half of the descending colon were displaced downwards and inwards, apparently by a mass in the right hypochondrium. Blood Kahn reaction was negative. Red blood cells, 5,216,000, hemoglobin, 94%, white blood cells, 11,100, polymorphonuclears, 78%. Urinalysis essentially negative. Van den Bergh normal delayed reaction, normal quantitative estimation. A provisional diagnosis of primary carcinoma of the liver was made and on March 21, 1931, an exploratory laparotomy was performed, confirming this diagnosis. The patient became progressively weaker and emaciated, with quite frequent drenching night sweats, and expired May 4, 1931.

Autopsy findings The body was that of a fairly well developed but extremely emaciated white male, 57 years of age. There was little of note on external examination beyond the presence of an old long right rectus incision, healed, and a nodular mass in the right upper quadrant of the abdomen. The dome of the diaphragm on the right reached to the fourth rib. Pleural cavities were free, however, and the right lung was emphysematous throughout and showed an occasional

small plaque-like half-bean-sized greyish-pink subcapsular nodule, these nodules were also seen in the left lung. The posterior half of the left lower lobe was edematous, congested, and showed scattered bronchopneumonic areas. The heart was of normal size and showed relatively little of note grossly. The liver extended 9 cms below the right costal border, 2 cms below the left costal border, and 3 cms below the ensiform in the midline. The upper limit of its right lobe was, as before stated, at the level of the fourth rib. The liver weighed 3,860 grms. It was markedly nodular, studded with innumerable greyish-white, relatively soft, somewhat rubbery nodules, varying from a filbert to a grapefruit in size. The right lobe was chiefly involved and its lower border, posteriorly, was at the crest of the ilium. It was markedly adherent to the cecum and hepatic flexure which were pushed anteriorly and medially by the growth. The gall bladder was small but grossly intact. On section these nodules were seen to be very extensively degenerated, especially the larger ones, and presented varying colors—some were yellowish, others more greyish-white, and still others showed extensive hemorrhagic extravasation. The smaller ones showed an outer rim of relatively well preserved tissue with central areas of degeneration. A few perigastric and pre-aortic involved glands were present. The gastro-intestinal tract was negative throughout. The pancreas, though adherent to the undersurface of the growth, showed no evidence of neoplasm. Spleen, kidneys and adrenals were also quite innocent of any neoplastic process and showed relatively a normal gross appearance. The bladder and prostate were also negative. The brain was examined and no evidence of pathology found. This was evidently a primary carcinoma of the liver with metastases to regional lymph glands and lungs, and terminal bronchopneumonia in the left lower lobe.

Microscopic findings A large number of sections were taken through the various portions of the liver and through the small plaque-like nodules in the lungs and involved regional glands. They showed a neoplastic process, characterized by very large more or

less spherical, deeply-staining cells of atypical epithelial form. Mitotic figures were frequent but no tendency toward giant cell formation was evident. The cells were frequently arranged in columns with spaces between. A very sparse fine trabecular stroma was present and where the liver tissue was incorporated there was a definite but relatively slight cirrhosis. The spaces mentioned above were evidently aborted attempts at duct formation. Extensive fatty infiltration and considerable hemorrhagic extravasation was also present. The sections through the glands and nodules in the lungs showed a process similar to the above.

Diagnosis Primary carcinoma of the liver (cholangioma type), with cirrhosis. Metastases to lungs and regional lymph glands.

COMMENT

Sex and Age All twelve cases occurred in males. We see a much smaller number of Chinese women in proportion to men than is true in whites. This is not sufficient to explain the great frequency of primary carcinoma of liver in males. Our impression is that some additional environmental factor must play a part in the causation of this condition. The average age was 46.5 with extremes of 21 to 76 years.

TABLE III
Age Incidence

DECADE	CHINESE	WHITE
21 to 30	1	0
31 to 40	2	0
41 to 50	5	0
51 to 60	2	1
61 to 70	0	0
71 to 80	0	1
	<hr/> 10	<hr/> 2

It is interesting that 5 of the 10 Chinese cases occurred in the fifth decade.

Symptoms There are no symptoms characteristic of primary carcinoma of the liver. The patients usually present the clinical picture of a rapidly progressive cirrhosis of the liver with un-

usually speedy emaciation. Edema of the extremities commonly occurs and ascites is usual. Jaundice occurs in some cases but is not constant. The high fixed liver may be a suggestive factor in the diagnosis. This was noted in a number of our cases. It was especially well shown in case I in which a radiograph of the chest showed the right diaphragm up to the second rib. The liver was fixed and did not descend with inspiration or changes in posture.

Antemortem diagnosis of primary carcinoma of liver was made in two cases, I and XII in this series. In case I this was made entirely on clinical evidence and on the negative laboratory findings. The high fixed liver was a noticeable feature here. In case XII the antemortem diagnosis was confirmed by an exploratory laparotomy and biopsy.

PATHOLOGY

Primary carcinoma of the liver may be divided into two types on the basis of the cellular pathologic changes: (1) hepatoma, a true liver cell tumor, and (2) cholangioma, a bile duct tumor.

In this series there were eight hepatomas and four cholangiomas.

The relation of cirrhosis to primary carcinoma of the liver is definitely established. Some observers go so far as to question the diagnosis of a primary carcinoma of the liver in the absence of a definite cirrhosis. The cirrhosis may be either portal or biliary and is probably a precursor of the carcinoma. In cirrhosis, a degeneration of the liver cells and bile ducts occurs followed by some evidence of regeneration or attempts at regeneration which may re-

sult in the disorderly growth which characterizes these carcinomas Eggel⁴ found cirrhosis in 85 per cent of hepatomas and 50 per cent of cholangiomas. In our series, cirrhosis was present in all four of the cholangiomas and in seven of the eight hepatomas, the exception being in one of the white patients in the series. The microscopic sections in this case were so definitely those of a true hepatoma that we have no hesitation in including it in this series in spite of the absence of the usual cirrhosis.

Metastasis appears to occur entirely by the blood stream. The hepatomas invade the capillaries and gross tumor emboli are frequently seen in these cases in portal vein radicles and in the inferior vena cava. The cholangiomas are said to metastasize earlier and more frequently than the hepatomas. In this series, however, metastases were more frequent among the hepatomas, occurring in five of the eight cases and being found in only two of the four cholangiomas. The lungs were involved in five cases, the ribs and spleen in one case, the mesenteric and perigastric glands in two, and the brain in one.

While nothing has been added to our knowledge of primary carcinoma of the liver by this contribution it seemed worthy of record (1) because of the rather large number of cases of a comparatively rare condition, and (2) because of the high incidence in the Chinese. This increased incidence in the Chinese in our series is, we believe, a result of the fact that these immigrants come from Kwangtung, a province in China where chronic disease of the liver and primary carcinoma of the liver are of more frequent occurrence,

than in other parts of China. Infection with *Clonorchis sinensis* may have been the exciting factor in the production of some of these primary carcinomas while others may have resulted from chronic irritation of the liver due to other causes (hepatitis with resulting cirrhosis). While the actual parasites were not found in any of our cases, the infection with *Clonorchis* is after all only the exciting factor, the parasites setting up a chronic irritation resulting in a cirrhosis and in some cases in primary carcinoma.

In an autopsy on a Japanese male, aged 46, we found an extensive involvement of the liver with *Clonorchis sinensis* which had converted it into a more or less polycystic, markedly degenerated structure, these cyst formations being dilated biliary channels. Histologically, definite evidence of cirrhosis, bile duct and slight liver cell regeneration was apparent. This seems of interest in the possible correlation of cirrhosis of the liver with primary carcinoma, for, as Maxwell states from personal knowledge, primary carcinoma of the liver is common in certain limited areas in China where *Clonorchis* infection is common.

In the past three months we have found a coincident *Clonorchis* infection in a Chinese woman dying of a miliary tuberculosis and in a Chinese male dying of massive hemorrhage from gastric ulcer. These had produced no gross pathologic change in the liver and on histological examination showed only a chronic cholangitis. It seems probable that had these patients lived, a more definite cirrhotic process might have been established.

The liver in one of our white cases

showed no cirrhosis but in the other, case XII, there was a very slight degree. This is of interest as this man had lived in India on a tea plantation for 20 years and gave a history of malaria and, apparently, dysentery, and there is a likelihood of his having had some parasitic infection while there.

CONCLUSION

1 A series of twelve cases of primary carcinoma of the liver is presented. Ten of these are in Chinese and two in whites. These were observed at the Vancouver General Hospital in the twelve years, 1920 to 1931, inclusive.

2 The incidence of the series as a whole was 12 cases in 1967 autopsies, or 0.61 per cent. The incidence in whites was: 2 cases in 1828 autopsies, or 0.109 per cent. The incidence in Chinese was 10 cases in 139 autopsies, or 7.19 per cent.

3 The Chinese came entirely from the province of Kwangtung in the

south of China. Investigations have shown that in that area as high as 100 per cent of the population are infested with intestinal parasites. The commonest is the liver fluke, *Clonorchis sinensis*. All of these cases showed a cirrhosis suggesting previous chronic liver irritation.

The high incidence of primary carcinoma of the liver in these Chinese may, we believe, be a result of the frequent infestation with intestinal parasites.

5 Eight of the twelve cases were hepatomas or liver cell carcinomas. Four were cholangiomas or bile duct cell carcinomas.

BIBLIOGRAPHY

- ¹STRONG, G. F., and PITTS, H. H. Primary carcinoma of the liver, *Arch. Int. Med.*, 1930, xli, 105-120.
- ²COUNSELLOR, V. S., and MCINDOE, A. H. Primary carcinoma of the liver, *Arch. Int. Med.*, 1928, xxxvii, 363-387.
- ³MAXWELL, J. L. Cancer among the Chinese, *China Med. Jr.*, 1928, xliii, 69-80.
- ⁴EGGER, H. Quoted by Counsellor and McIndoe.

Some Recent Observations Regarding the Nature of Epilepsy

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INTRODUCTION

A SURVEY of the literature on the subject reveals the fact that there has been a notable revival of interest in the problem of epilepsy during the past few years. Although the annals of medical history are replete with references to this bizarre convulsive disorder, there have been but two short periods before the present in which measurable progress toward solution of its problems has been made. The first of these was that in which the illustrious Greek physician, Hippocrates (460-347 B C)¹ succeeded in dissipating the cloud of superstition that had previously enshrouded the disease and laid the foundation for our present conception regarding it. The second covered a span of approximately thirty years (1855-1885), during which Laycock² introduced bromide therapy and Kussmaul and Tenner,³ Jackson,⁴ Gowers⁵ and others made a vigorous attack upon the problem of pathogenesis using both clinical and experimental methods.

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Of special interest to us here is the fact that these early investigators expressed certain views regarding the nature of the disease which are similar to those held by leading neuropathologists today.^{6,7} In his plea for recognition of the fact that epilepsy is not a "sacred" disease but, like any other disorder of the body, has a natural cause, Hippocrates finally concluded that "whoever is acquainted with such a change in men and can render a man humid and dry, hot and cold by regimen could also cure this disease." Regarding the relative importance of various causative factors Kussmaul and Tenner (1859) made the following statement: "Every physician of the present day who is at all judicious will relinquish the hope cherished with childlike confidence by certain schools and times that pathological anatomy is destined to give an explanation of the nature and seat of epilepsy, and he will only expect that result from the progress of the experimental physiology of nerves." Gowers held a similar opinion, stating that, "It is a disease of tissue, not of structure." He was convinced that final solution of the problem must await further advances in brain cell physiology.

Among the contributions made during the present period have been the

following (1) The introduction of phenylethylbarbituric acid as a specific remedial agent; (2) the observation that marked symptomatic improvement results from fasting⁹ or from the use of a ketogenic diet,^{10,11} and the discovery that certain factors, such as the state of oxygenation of the blood,⁶ the acid-base equilibrium^{12,13,6,11} and the water balance of the body^{15,16} may greatly influence the occurrence of seizures. In their recent monograph on the subject Lennox and Cobb⁶ summarize the present status of the problem as follows "The physiological changes which we have mentioned (anoxemia, alkalosis and edema) are themselves only contributory factors. They tend to induce seizures by increasing the irritability of nervous tissues, producing an effect which is not specific for epilepsy. Furthermore, the physiological changes mentioned will produce seizures only in those who are subject to seizures. Therefore, the question yet remains, why, under a given stimulus, one person should have a seizure and another not. . . Though this variability is presumably related to the subtle chemistry of the brain cell, its elucidation is for the future. As we have emphasized above, there is no constant anatomical lesion in epilepsy, and only a minority of all patients with extensive cerebral pathology have fits. We are forced then to postulate some unknown constitutional element. This abnormal 'convulsive capacity' is presumably present in some degree in each person with epilepsy."

The purpose of the present paper is to review some of the data from several of our recent studies, which were undertaken primarily with the hope of

obtaining information regarding the basic nature of the elusive functional pathology ("nervous instability") upon which this "abnormal convulsive capacity" is dependent. Our experimental approach to the problem has been that of attempting to elucidate the mechanisms by which epileptic convulsions are either induced or prevented from occurring by certain changes in regimen. The particular studies presented here concern the relationship of water and mineral metabolism to the occurrence of seizures. While evidence obtained by this indirect method must of necessity be incomplete and more or less presumptive in character, it is obvious that any data whatsoever, which point to a disturbance in brain cell physiology, may be important for the ultimate solution of the problem.

RESULTS

Examples of data from two different series of clinical experiments are presented in detail on the accompanying graphic charts which are largely self-explanatory. They have been selected from a more extensive study on the water and mineral metabolism^{17,18} to illustrate several points of difference between the reaction of the epileptic and that of the normal subject under given conditions.

These conditions and the methods of procedure used were essentially as follows. Each experimental subject was kept in a small metabolism ward in company with another patient under the constant supervision of a well-trained special nurse. He was kept in bed under light covers continuously except for short periods when allowed up to use the bed-side commode and to be

weighed The room temperature was kept between 20° and 24°C and the relative humidity between 40 and 66 per cent so that there was no sensible sweating Each day was divided into four six-hour periods in each of which the diet, water intake and medication were the same At the end of each six-hour period the bladder was completely emptied into a weighed container, after which the net body weight was determined on an accurate scale sensitive to five grams The food, water and medication for the next period were then given The diet for the first patient (chart I), which was uniform throughout the study, consisted of distilled water, cane sugar, egg yolk, egg white, fresh 40 per cent cream, clear lemon juice and whole-milk powder — substances of comparatively constant composition which lend themselves to accurate analyses In the second experiment (chart II), heavy cream and cane

sugar alone were given because it was desired in this instance to have a still lower mineral intake The complete water balance was measured according to the method described by Newburg and Johnston ¹⁹

The experiments shown on chart I illustrate the effect of induced changes in the state of hydration of the body upon the mineral exchange and the occurrence of convulsive seizures in an epileptic girl fourteen years of age This particular patient was selected for the study because of the great severity of her epilepsy (2 to 12 convulsions daily when not under treatment) and because she had previously been found to be amenable to luminal therapy and was extremely sensitive to alterations in her water balance She was given a maintenance diet with sufficient water to satisfy her thirst and her physiological requirements under ordinary conditions, as determined by a three-day pre-

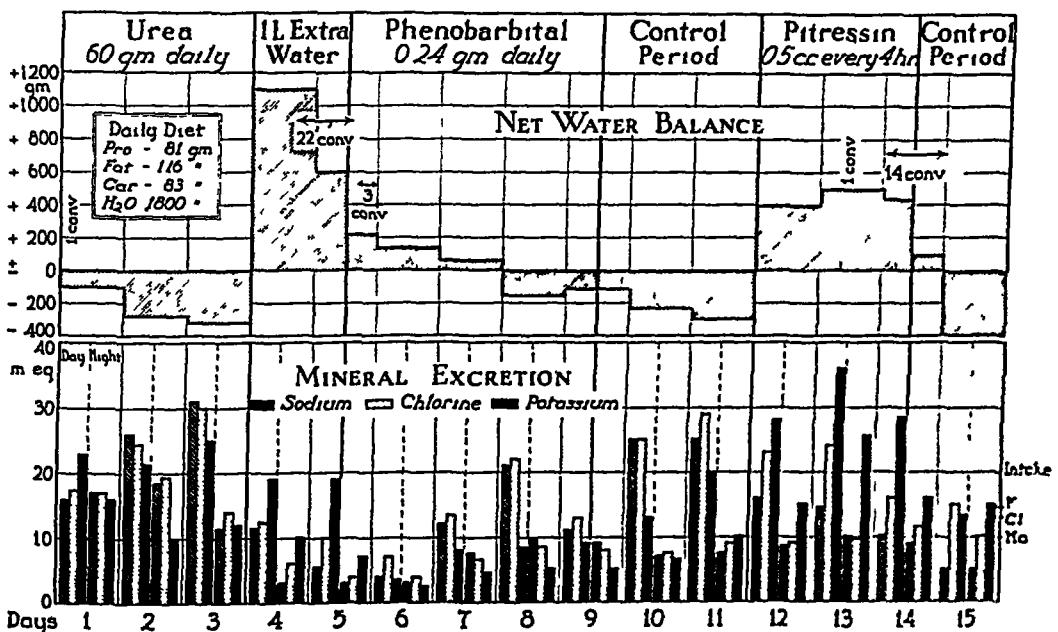


CHART I Relationship of water and mineral balances to the occurrence of convulsions under various conditions

liminary period, not included in the chart. The single variable factor for each distinct period is indicated at the top of the chart.

The close relationship between the water balance of the body and the occurrence of seizures was the most striking observation of this study. It is obvious that sudden storage of water was followed within from 18 to 36 hours by numerous *grand mal* attacks, whereas a negative balance from any cause was followed fairly promptly by their cessation. In respect to the mineral balance, the most important results were those pertaining to the excretion of potassium and sodium. The contrast between the non-convulsive and the convulsive periods, as regards the ratio of urinary K to urinary Na was striking. In all but the last period Na predominated during periods of negative water balance with freedom from seizures, whereas the excretion of K greatly exceeded that of Na during the convulsive periods. The ratio

$$\frac{\text{m eq K}}{\text{m eq Na}}$$

for each of the experimental periods was as follows: Urea period, 0.8; first water storage period, 2.5; phenobarbital period, 0.6; control period, 0.7; and pitressin period, 2.3. From the viewpoint of the pathogenesis of seizures these facts appear to us to be of considerable significance. When the large negative balance of K for the water storage periods was first recognized, it was casually looked upon as being merely secondary to the convulsions, that is, it was interpreted as representing nothing more than an attempt on the part of the tissues to furnish base

for neutralization of the H_2CO_3 and lactic acid accumulating in the body fluids during the seizures. The objection to this assumption, however, is the fact that the increase in K output manifested itself from 12 to 36 hours before the first convulsion of each series, at a time when water was being stored. This phenomenon was particularly striking during the pitressin antidiuresis period where it preceded the first convulsion by more than 36 hours.

Since in the human subject most of the K of the body is held within, and most of the Na outside, of the cells, as determined by the semipermeability of the cell membranes, it appears clear to us that the preponderance of Na and Cl in the periods of diuresis indicates removal of extracellular fluid; whereas, excessive excretion of K, as during the pitressin period, indicates a "leakage" of this element from within the body cells. This response to pituitary antidiuresis has not been seen in normal subjects nor in mildly epileptic patients in whom the procedure has not been pushed to the point of inducing seizures. In fact, normal subjects taking the diet given here show a predominance of Na and Cl excretion during pitressin antidiuresis. The amount of K in the pituitary extract is far too small to be a significant factor in the increased K output. It is interesting that K and Cl instead of Na and Cl predominated in the extra water eliminated in the post-pitressin period. This may be interpreted as indicating that stored extracellular water contained a considerable amount of K which had diffused into it from the cells during the pitressin period or that some of the water retained had been stored within

the cells and had carried K with it as it was expelled from them following the disappearance of the pitressin effect

The water and mineral exchanges during the period of intensive phenobarbital therapy were of special interest. The body weight, which had risen very rapidly during the preceding period of forced water drinking continued to increase slightly during the first three days with storage of small amounts of the various minerals. At the end of the second day the patient showed fairly marked puffiness of the face and definite pitting edema over the legs but with normal urine findings and no signs of myocardial insufficiency. This disappeared following the occurrence of a spontaneous diuresis, which began on the third day and reached its height during the post-phenobarbital

control period. The appearance of this subcutaneous edema, which cannot be adequately explained by the comparatively small magnitude of the positive water and mineral balances on these two days, suggests the possibility of a translocation of water from the intra- to the extracellular position.

Observations similar to the foregoing on the relationship of water storage to the occurrence of *grand mal* seizures in severely epileptic patients suggested the type of experiment represented on chart II. It was assumed that a more or less crucial test of the fundamental importance of this relationship in the disease would be the response of mildly epileptic patients to forced water drinking and simultaneous pituitary antidiuresis during their free intervals between regular attacks. Experiments

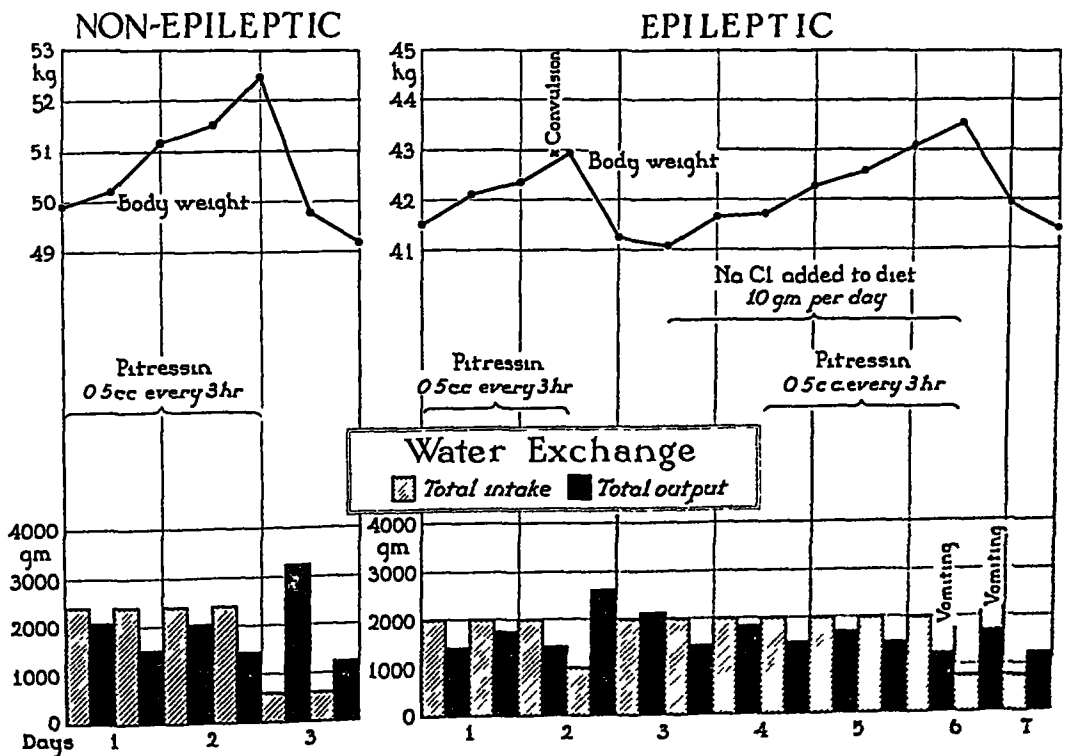


CHART II Effect of sustained pituitary antidiuresis on epileptic and non-epileptic subjects

undertaken with this in mind demonstrated that it is possible in a high percentage of cases to induce typical *grand mal* seizures (and very occasionally *petit mal*) by this procedure. Non-epileptic subjects of a similar age group have failed to have seizures of any kind when treated in the same or an even more rigorous manner. The results thus far suggest that the test is more or less specific in bringing out at least one characteristic weakness in the physiological adjustment of the epileptic patient, even when this is latent.

The data presented in chart II are typical in showing the contrast between the response of the non-epileptic and that of the epileptic subject to sustained pituitary antidiuresis. When both were placed on extremely low mineral diets and were given the amounts of water indicated and at the same time sufficient pitressin subcutaneously to prevent water diuresis, the mild epileptic had a typical seizure at the end of thirty hours and after a gain of only 1.5 kilograms, or 3 per cent, in body weight, whereas the non-epileptic had no convulsive reaction in spite of a gain of 2.5 kilograms, or more than 5 per cent, in body weight. The latter experienced much more abdominal discomfort, nausea and malaise before her test was completed than did the epileptic patient, which indicates that the control was sufficiently rigid.

Following the recovery of his water balance after the first test, the epileptic patient was again subjected to the procedure but this time with just sufficient NaCl added to the diet to prevent dilution of the extracellular body fluid by the retained water. As shown on the chart the effect of the latter mea-

sure was apparently to prevent the occurrence of a seizure even though the test was continued over 48 hours and 2.5 kilograms of water was retained as against 1.5 kilograms in the previous test. Several days later repetition of the procedure without addition of the salt was once more followed by a typical *grand mal* attack at the end of 18 hours. The resemblance between the reaction of the non-epileptic subject during the regular test and that of the epileptic, when extra NaCl was given, was striking to the last detail, except for the fact that the latter subject finally vomited after the procedure had been carried well beyond the point usually necessary for induction of seizures.

DISCUSSION

Although the data presented here are in themselves clear-cut, their interpretation in respect to the mechanism of the convulsive seizure must of necessity be highly tentative because the evidence is incomplete and is more or less inferential in character. Nevertheless, with these limitations definitely in mind, it is interesting to conjecture regarding the possible sequence of events which appear to lead up to the convulsion under the conditions of our experiments.

If we assume that epilepsy is a disorder of the nervous system in which there is an inherent disturbance in brain cell physiology, what particular function of the cell may be deficient? Having practically ruled out increased intracranial pressure and the vasopressor action of the pituitary extract as primary factors in the causation of seizures in the antidiuresis experiments,¹⁷ we believe that such data as we have

here may indicate an inherent weakness in the mechanism for controlling the semipermeability of the brain cell membranes. When the subject, who has been on a low mineral diet for a number of days, is forced by sustained antidiuresis to retain a volume of distilled water equal to from 3 to 6 per cent of his original body weight, a significant decrease in the total osmolar concentration of the electrolytes in his extracellular body fluids is found to occur. Under these conditions there is undoubtedly a strong tendency for an excess of water to enter the fixed cells of the brain and other organs and for intracellular elements to diffuse outward because of the lowered osmotic pressure of the fluid outside of the cell.

From the data presented, it appears that the normal subject can temporarily withstand the strain of this rather drastic modification of the extracellular fluid, whereas the epileptic's margin of protection is much narrower. We have pictured the situation tentatively somewhat as follows. The chemical structure of the brain cell membrane may be deficient or the cell colloids as a whole may be abnormal in their constitution or in their mutual relationships. Variability in clinical severity might well be determined then by the type and degree of abnormality present. In the case of the severely epileptic patient, (chart I) not only sustained pituitary antidiuresis, but the mere drinking of extra water following a period of dehydration resulted in the occurrence of many seizures. The mechanism here is probably the same as in the mild case (chart II) in which a convulsion was induced, namely, that extra water enters the cells and K diffuses from them

at the same time because of functional inefficiency in the cell membranes. It is conceivable that the resulting disturbance in the equilibrium between the various electrolytes and the imbibition of extra water by the cell colloids would account for the wide-spread irritability of the brain cells. The assumed imbibition of water by the brain cells with simultaneous loss of K has its analogy in the experimental observation of MacDonald,²⁰ that nerve tissue in Ringer's solution swells and loses K by diffusion at a point of stimulation or injury. It is known from the work of Syz²¹ and others that any form of excitation or injury increases cell membrane permeability. Most factors which increase cell membrane permeability probably increase excitability also.

Whether or not a disturbance in membrane activity, such as that postulated here for the purpose of discussion, would be more likely to depend upon a defect in the chemical structure of the brain cells or upon extrinsic nervous or hormonal factors cannot be said from the data now available. We have some evidence of a disturbance in the ratio of lecithin to cholesterol in the blood plasma in relationship to seizures.²² This may indicate an abnormal state of equilibrium between these physiologically antagonistic substances in the brain tissue, which is characteristically rich in them. While there was found no constant relationship between the occurrence of seizures and the absolute level of either cholesterol or lecithin, the ratio of the latter to the former was found repeatedly to be highest at or very near the time of a convulsion and lowest at the time most remote from one, when samples were taken

serially on an individual patient. In the light of the fact that lecithin and cholesterol are considered to play a major rôle in the regulation of cell membrane permeability,²³ these data tend to support the idea of defective cell structure. Comparative brain analyses are at present being made for further testing this possibility. There are facts, on the other hand, which indirectly suggest the alternative explanation of a disturbance in the extrinsic nervous or hormonal factors governing permeability. Further investigation in this field is urgently needed.

In favor of the view that the characteristic convulsive tendency of the epileptic is dependent upon an inherent defect in the mechanism for controlling this important cell function, is the circumstance that various factors (narcosis, sedation, etc.), which favor cessation of seizures, are known to decrease permeability, while those which favor their occurrence (alkalosis, anoxemia, injury, stimulation) are known to increase it. On the basis of general considerations such as the latter, Georgi²⁴ has already elaborated a theory of increased cell membrane permeability in this disease. While our evidence is inadequate at the present time for formulation of a definite theory, we believe that the final solution of the epilepsy riddle will be found in some such abnormality of brain cell function as that suggested above.

SUMMARY AND CONCLUSIONS

1 Experimental and clinical studies on the relationship of epileptic seizures to variations in the water and mineral exchanges of the body are briefly reviewed

2. Production of a deficit in the body water by any means tends to cause a temporary cessation of convulsions in severely epileptic children

3. Re-establishment of a positive water balance results in recurrence of seizures in such patients

4. Typical *grand mal* attacks can be induced in a high percentage of the mildly epileptic patients, but not in non-epileptic subjects, by giving water at the rate of from 2 to 5 cc per kilogram of body weight per hour while maintaining effective pituitary antidiuresis. This difference in response between non-epileptic and epileptic patients appears to be sufficiently specific to serve as a test in differential diagnosis in obscure cases

5. Dilution of the extracellular body fluids is considered to be essential to the induction of seizures under these conditions, because addition to the low-mineral diet of just sufficient NaCl to prevent dilution tends to prevent their occurrence

6. Mineral studies show that during periods of diuresis and freedom from seizures the excretion of Na and Cl greatly exceeds that of K.

7. In one series of experiments it was found that the K balance was strongly negative during convulsive periods, when water was being stored. At the same time Na showed a slightly positive balance

8. Since most of the K of the human body is held within the cells, this marked increase in K excretion, which manifested itself in the case of the severe epileptic from 2 to 36 hours before convulsions began to occur, indicates a "leakage" through the cell membrane. This phenomenon has not

been found to occur in normal subjects under similar conditions

9 These and other data referred to are tentatively interpreted as favoring

the view that the mechanism for controlling the semipermeability of the brain cell membranes is inherently defective in epilepsy

REFERENCES

- ¹ADAMS F The genuine works of Hippocrates, 1886, William Wood and Company, New York
- ²TALBOT, F B Treatment of epilepsy, 1930, The Macmillan Company, New York
- ³KUSSMAUL, A, and TENNER, A Referred to by Lennox and Cobb 1c
- ⁴JACKSON, J H West Riding Lunatic Asylum reports, 1873, iii, 315
- ⁵GOWERS, W R Epilepsy and other chronic convulsive diseases, 1881, J and A Churchill, London
- ⁶LENNOX, W G, and COBB, S Epilepsy from standpoint of physiology and treatment, Med, 1928, vii, 105-290
- ⁷HOLMES, E G The epilepsies, Brit Med Jr, 1929, ii, 260-261
- ⁸GUELPA, G, and MARIE, A Lutte contre l'épilepsie par la desintoxication, Bull Gen de Therap, 1910, clx, 616-624
- ⁹GEYELIN, H R Fasting as a method for treating epilepsy, Med Rec, cix, 1037-1039
- ¹⁰WILDER, R M The effects of ketonuria on the course of epilepsy, Mayo Clin Bull, 1921, ii, 307
- ¹¹PETERMANN, M G Ketogenic diet in treatment of epilepsy, Am Jr Dis Child, 1924, xxviii, 28-33
- ¹²JARLOV, E Sur l'equilibre acido-basique du sang humain etudie dans ses rapports avec diverses affections, Compt rend Soc de biol, 1921, lxxiv, 156-158
- ¹³GEYELIN, H R, BIGWOOD, E J, and WHEATLEY, M A The reaction of blood in epilepsy, Proc Soc Exper Biol and Med, 1923, xxi, 227-228
- ¹⁴MCQUARRIE, I, and KRITH, H M Experimental study of acid-base equilibrium in children with idiopathic epilepsy, Am Jr Dis Child, 1929, lxxvii, 261-277
- ¹⁵FAY, T Some factors in mechanical theory of epilepsy, with especial reference to influence of fluid, and its control, in treatment of certain cases, Am Jr Psychiat, 1929, viii, 783-835
- ¹⁶MCQUARRIE, I Epilepsy in children, relationship of water balance to occurrence of seizures, Am Jr Dis Child, 1929, xxxviii, 451-467
- ¹⁷MCQUARRIE, I and PEELER, D B Effects of sustained pituitary antidiuresis and forced water drinking in epileptic children, diagnostic and etiologic study, Jr Clin Invest, 1931, x, 915-940
- ¹⁸MCQUARRIE, I, MANCHESTER, R C, and HUSTED, C Study of the water and mineral balances in epileptic children, Am Jr Dis Child, 1932, xliii, 1519-1543
- ¹⁹NEWBURGH, L H, JOHNSTON, M W, and FALCON-LESSES, M Measurement of total water exchange, Jr Clin Invest, 1930, viii, 161-196
- ²⁰MACDONALD, J S Migration of potassium and the injury current, Proc Physiological Soc, Jr Physiol, 1905, xxvii, 66-67
- ²¹SIZ, H C Entrance of convulsant dyes into substance of brain and spinal cord after injury to these structures, Jr Pharm and Exper Therap, 1923, xxi, 263-290 Observations on experimental convulsions with special reference to permeability changes, Am Jr Psychiat, 1927, vii, 209-219
- ²²MCQUARRIE, I, BLOOR, W R, PATTERSON, H A, and HUSTED, C The possible significance of changes in blood lipids in epilepsy, Am Jr Dis Child, Soc Trans, 1931, xlii, 720-721
- ²³LEATHES, J B Role of fats in vital phenomena, Lancet, 1925, i, 803-807, 853-856, 957-962, 1019-1022
- ²⁴GEORGI, T Zur Pathogenese des epileptischen Anfalls Deutsch Ztschr f Nervenhe, 1926 lxxviii, 126-127

Modern Muscle Physiology and Circulatory Failure

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THE prevailing interpretation of circulatory failure, particularly when conceived as cardiac in origin, is usually founded upon an anatomical concept, the reason most probably being that the special senses are appealed to. The murmurs produced by valvular defects are readily heard or felt. The irregularities of rhythm are likewise recognizable either by palpation of the pulse or by graphic records such as the electrocardiograph. The rest of the disorders or deficiencies of function are covered by that all-embracing term, myocarditis. What this exactly means is hard to define and the term has probably done more to retard our investigation of circulatory disease than any other single factor. The cardiac muscle, the very main-spring of the circulatory system, has received but scant attention. It is a fact that whereas twenty years ago the stethoscope was the last court of appeal in cardiac diagnosis, now the electrocardiograph is the main arbiter. But no matter how meticulously the QRS and T deflections are studied the knowledge so obtained is but limited and what is worse it becomes almost Delphic in its oracular dogmatism, platitude being piled upon platitude.

Unless we continue to seek the complete truth of why cardiac muscle fails, the full understanding of circulatory disease can progress but little.

There is probably no realm of physiology that has attracted more attention during the past twenty years than has the elucidation of muscle contraction. The search for truth has been pursued with a single-mindedness of purpose, a generosity in controversy, and an open acknowledgment of mistakes that is seldom seen in scientific disputes but which is much to be emulated. This knowledge must now be applied to the pathological physiology of the heart. This is not the place to enter into a detailed description of the most modern conception of muscle physiology, but a brief account is necessary.

The primary constituents for muscle contraction are a labile form of organic phosphate called "phosphagen" and glycogen. The glycogen is obtained from the blood glucose through the action of insulin and oxygen. On contraction the glycogen is broken down into lactic acid and the amount of lactic acid is proportionate to the amount of muscular energy developed. In mammals there is no evidence that lactic acid is directly resynthesized into glycogen in the muscle, but it is carried to the liver where it is reformed into glycogen and re-enters the blood as glucose.

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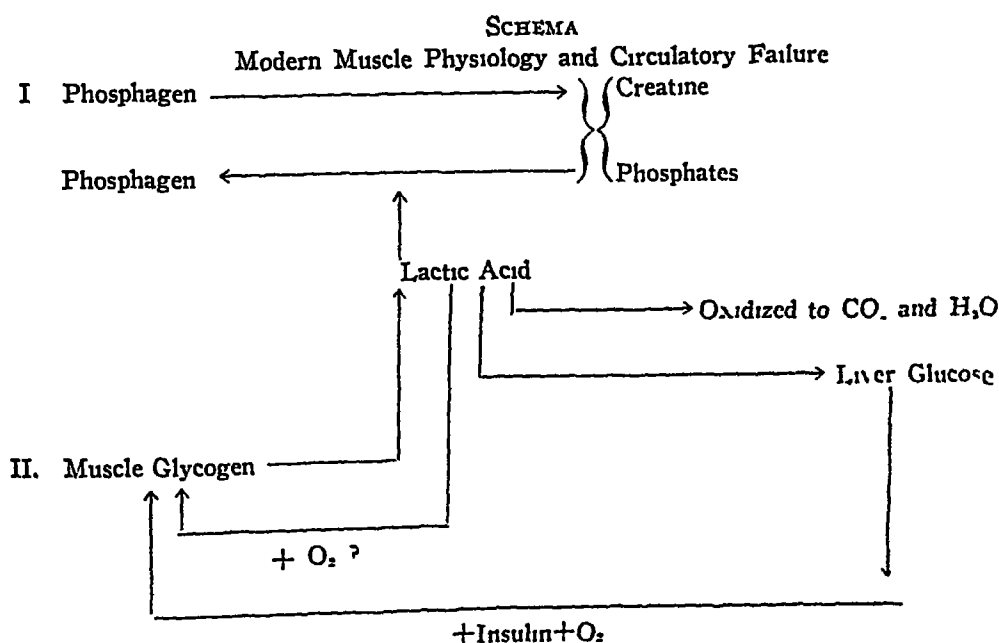
In addition, the pre-existing stores of carbohydrate in the liver are also discharged during the recovery period to be carried to the muscle as glucose, from which muscle glycogen is produced and stored locally. This last conversion requires the participation of insulin and oxygen.

Although lactic acid formation may be taken as an index of energy it does not occur immediately. During muscular contraction "phosphagen" is broken down into creatine and phosphate. This is the primary change by which energy is set free. It is after the contraction that lactic acid appears and during the period when the "phosphagen" is restored. The energy liberated by delayed lactic acid formation allows re-synthesis of "phosphagen", this, however, does not occur if lactic acid formation is impossible, as in a carbohydrate-free muscle, or in muscles poisoned with iodoacetic acid.

Such in very brief is our knowledge

of muscle physiology. In what manner can this be used to elucidate some of our problems of cardiac deficiency? As yet but little is known about variations in "phosphagen". So for the present our attention must be confined to a study of glycogen metabolism as this is such an important adjunct in "phosphagen" reactions.

During the past few years workers in our Department have directed their attention to this important subject. It will be noted from the schema that the vulnerable points in the glycogen-lactic acid cycle are in the conversion of lactic acid into glucose in the liver and that of the blood glucose into muscle glycogen by insulin and oxygen. It is not my purpose to go into all the possible causes whereby this cycle may be interrupted, but to confine my remarks to a number which are particularly pertinent to important problems in clinical medicine.



NORMAL VARIATIONS IN CARDIAC GLYCOGEN

It is known that cardiac muscle ordinarily contains a relatively high percentage of glycogen and that it is zealously conserved in a variety of conditions when the skeletal muscle glycogen reaches a low level. A good example is the high percentage of glycogen in the heart in diabetes whereas it diminishes considerably in the skeletal muscles in this disease. Kilbourn and MacLeod¹ demonstrated another interesting fact in that the primitive heart of the dogfish contains much more glycogen than the skeletal muscles or even the liver. The percentage of glycogen in the heart and in the skeletal muscles is not always in the same ratio. MacLeod and Prendergast² found in the dog that the heart percentage was the greater while in rabbits it was the reverse. Katz, Kerridge and Long³ also found in cats that the percentage in the skeletal muscle was the greater. But these ratios are not necessarily constant as MacLeod and Prendergast² demonstrated that during starvation the skeletal muscle glycogen decreased while the cardiac glycogen remained unchanged or even appeared to increase. This has been confirmed in rats by Lawrence and McCance.⁴ This would seem to indicate that cardiac glycogen would remain until other deposits were exhausted.

CARDIAC WORK AND GLYCOGEN CONTENT

Under normal conditions it has been found impossible to reduce the cardiac glycogen by direct energy demands provided there is an adequate supply of oxygen. G. T. Evans,⁵ in our Depart-

ment, has demonstrated this by exercising rats to an extreme extent and under no conditions of physical exercise without anoxemia was the cardiac glycogen below the normal resting levels. He has also shown that adrenalin injected intravenously in doses sufficient to produce a pronounced rise of blood pressure and a profound increase of cardiac rate does not deplete the cardiac glycogen content. This work was done with rats. It is conceivable that a tachycardia could be produced which might shorten the recovery period to such an extent as to interfere with the normal physiological cycle. As yet this has not been accomplished by this means and is probably more likely to be found in the hearts of larger animals.

OXYGEN CONSUMPTION

Experiments by Lovatt Evans⁷ and his co-workers have shown that the oxygen consumption of the heart is in proportion to the work done. When this is increased as by the injection of adrenalin the oxygen consumption likewise increases. Starling and Visscher⁸ have demonstrated that the oxygen consumption of the heart is determined by the diastolic volume and therefore by the initial length of the muscle fibres. In other words, under physiological conditions the oxygen consumption at a given diastolic volume is always the same but has no relation to the systolic volume. In reference to rate they found that a slow heart can do a given amount of work per unit of time more economically. But as the heart tires and its functional capacity decreases, its mechanical efficiency is diminished, i.e., although the total energy (as measured by oxygen consumption) liberat-

ed at any given initial length of fiber remains unchanged, the fraction of this energy which can be utilized for the performance of work progressively diminishes. To do the same amount of work the heart has therefore to dilate continuously, and the work is maintained constant at an ever-increasing cost in total energy.

GLUCOSE AND INSULIN REQUIREMENTS

The earlier works on the glucose requirements of the heart were undertaken before the present knowledge of muscle physiology and insulin was known and also before the present technique of the isolated heart-lung preparation was perfected. These early workers all came to the conclusion that glucose was utilized by the heart in the performance of work. The experiments of Bayliss, Muller and Starling⁴ definitely demonstrated that the RQ of the heart-lung preparation is 0.95. In order that the preparation may be kept in good condition for long periods it was necessary to introduce insulin and glucose. They found in the absence of the former that enormous concentrations of glucose were necessary to compensate for the insulin deficiency. They found that glucose without insulin did not disappear by combustion. Furthermore, insulin and glucose had no specific effect upon the metabolism since it changed only if cardiac work changed at the same time. In other words, insulin and glucose are necessary for efficient cardiac function which is dependent upon adequate glycogen supplies which are provided by these two substances plus oxygen. These results were confirmed by

Cruickshank and Shrivastava⁹ who established that the sugar utilization of the heart is increased by insulin and also by maintaining a high blood sugar concentration. They have also shown in the dog's heart that glycogen synthesis depends upon insulin dosage and blood sugar concentration. G. T. Evans⁵ has gone farther and has demonstrated in the rat's heart that the normal values of glycogen can be greatly increased by insulin and glucose so that the heart can be its own storehouse under proper conditions.

PATHOLOGICAL CONDITIONS

1 *Oxygen Deficiency* Katz and Long,¹⁰ using mammalian heart preparations, have shown that by reducing the oxygen supply to the heart there was rapid dilatation and failure of function. The contractions became feeble and conduction slower, but recovery was possible unless diastolic standstill had occurred. During some experiments undertaken in this Department to investigate circulatory failure caused by diphtheria toxin, G. T. Evans found that the striking feature was sudden death which could be prevented by artificial pulmonary ventilation. When this was not done and the heart removed rapidly just before death was expected, it was found that the heart was practically depleted of glycogen. In other words the sudden death appeared to be due to a respiratory failure with progressive anoxemia, producing a conspicuous reduction in cardiac glycogen. He pursued this point and found that the cardiac glycogen was practically wiped out in carbon monoxide poisoning and in acute asphyxia produced by occluding the

trachea This depletion may occur within a minute or so. He next attempted to find at what level of anoxemia this reduction occurred or whether it was a gradual process in proportion to the reduction in oxy-hemoglobin saturation. The easiest means of producing graded anoxemia is by reducing the oxygen percentage of the inspired air. He found that at 13, 11 and 9 per cent there was little or no change in the glycogen content of the cardiac muscle. Below 7 per cent, however, there was a reduction and below 6 per cent the glycogen was reduced to about one-third of the normal amount.

It has been appreciated for some time by both mountaineers and aviators that there is a critical level in high altitudes. This varies somewhat from man to man but in the most fit it is between 25,000 and 27,000 feet, or a barometric pressure around 300 mms which is equivalent to about 8 per cent oxygen in the inspired air and an alveolar oxygen of about 30 mms. Such an alveolar oxygen partial pressure after making allowance for a reduction of the CO_2 to 20 mms would saturate normal hemoglobin to about 70 per cent. It has been found in lobar pneumonia, bronchopneumonia, edema of the lungs and other acute respiratory causes of anoxemia that when the oxy-hemoglobin saturation is below 75 per cent serious circulatory symptoms arise and the patient seldom recovers.

These experiments have dealt entirely with oxygen want as represented by a blood supply adequate in amount but deficient in oxygen. There is, however, another group of cases which have to be considered, namely those in whom the blood saturation is adequate but

through some local condition in the coronary system a sufficient amount of blood cannot be carried to the muscle. The most outstanding examples are lesions due to inflammatory, degenerative or mechanical occlusion of the larger or smaller coronary vessels. Common examples are to be found in rheumatic or syphilitic myocardial disease, hypertension and arteriosclerosis. In all of these conditions the coronary blood supply is apt to become deficient when the cardiac capacity for work will progressively decline. But the most spectacular effects are produced by cyanide poisoning when, through sudden arrest of oxidation, muscle metabolism immediately ceases.

2. *Changes in pH (a) Acidosis* It has been shown by Katz and Long¹⁰ that with anoxemia there is a rapid accumulation of lactic acid in the muscles and circulating blood when pulmonary ventilation is obstructed. Whereas the skeletal muscle is capable of tolerating considerable quantities of lactic acid within it, the cardiac muscle has no such property. The mammalian heart becomes exhausted when lactic acid accumulates to an average concentration of 0.72 gm per cent, while in the skeletal muscle this may rise to an average of 0.252 gm per cent. Thus, in the heart the lactic acid content can increase only two and a half times over the resting or normal active muscle whereas in the skeletal muscle it may increase four and a half times. It would therefore appear as if the heart has a much greater susceptibility to accumulation of hydrogen ions and has a much poorer buffering power. This being the case, the cardiac muscle arrives at its critical pH much more quickly than

does the skeletal muscle. This is an important observation as it shows that the heart has a greater intolerance to oxygen debt.

On the other hand, experiments by G. T. Evans have shown that a rat can be placed in an atmosphere of eight per cent of CO_2 for three hours. This produced profound hyperpnea, but it is apparently so buffered that at the end of this period the cardiac glycogen has not been reduced below the normal average level. The two sets of experiments are, however, not comparable, as in the first instance the accumulation of lactic acid was brought about through oxygen want while in the second, oxygen want does not need to be considered.

In the experiments of Katz and Long it is to be presumed that there was in addition to the local muscle anoxemia a considerable increase in the lactic acid content of the myocardium. Therefore, it may be stated, other things being equal, that acidosis *per se* does not interfere with glycogen metabolism.

(b) *Alkalosis* G. T. Evans has shown that alkalosis up to the point which does not interfere with respiration produces no change in the cardiac glycogen, but if apnea or even deficient pulmonary ventilation ensues sufficient to produce an oxygen want, then cardiac glycogen rapidly declines. This result is not effective upon the heart *per se* as alkalosis but only indirectly through its interference with proper respiratory function.

Thyrototoxicosis That thyrotoxicosis has a profound influence upon the circulation is a well-known clinical observation. The exact mechanism whereby this is brought about insofar as the

heart is concerned is not so clearly understood. It has been shown by Andrus and his co-workers¹¹ that the heart of an animal intoxicated by thyroxin is far more sensitive to the withdrawal of oxygen than is the normal one. Similarly, they have shown that the amplitude of contraction is more easily depressed by sodium lactate than is the normal heart. Making a chemical examination of such organs both normal and intoxicated, it was found that in the latter the lactic acid was increased on the average by over 70 per cent, while the glycogen content was reduced by over 60 per cent. This would indicate that thyroxin had brought about an accumulation of lactic acid and a depletion of glycogen in the myocardium. These results have been confirmed by Lawrence and McCance⁶ who found that thyroid extract given by mouth reduces very greatly the glycogen of the heart and furthermore that the hyperthyroid heart is unable to replenish its glycogen stores even after high carbohydrate feeding. This is quite different from the skeletal muscle. As yet experiments have not been conducted to show what influence insulin plus carbohydrate might have in offsetting this important deficiency.

Diabetes Reference has already been made to the importance of insulin in the conversion of blood glucose into muscle glycogen. Cruickshank and Shrivastava⁹ have studied the action of insulin on the storage and utilization of sugar by the isolated normal and diabetic heart. They found that the diabetic heart perfused with diabetic blood did not utilize blood sugar and that this lost power was restored by perfusion with normal blood or by the

addition of insulin. And furthermore, that in the diabetic, insulin administered in physiological doses maintained the glycogen synthesis and brought the glycogen and muscle sugar-content towards the normal. It is quite clear from these experiments that insulin plays an important rôle in the maintenance of the cardiac glycogen.

Cardiac Disease The direct estimation of cardiac glycogen in those dying of heart disease is impossible unless the heart could be removed at the instant of death. It is unfortunate that glycolysis takes place so rapidly; otherwise, if glycogen were a more stable substance important direct observations would have been made long ere this. It is necessary, therefore, in attempting to reconstruct what is taking place in a human failing heart, to work in an indirect manner. There is no reason to doubt that in all conditions where there is a deficient oxygen supply to the myocardium either through desaturation of the blood that is supplied to the heart, or through interference with the quantity of blood that can reach the muscle, a reduction of cardiac glycogen occurs. The exact threshold of such depletion can not be determined, that every effort will be made to compensate for such, there is every reason to believe. But it is to be expected that there is a critical level beyond which it is dangerous to go. This has been shown in the case of acute anoxemia. Long and myself have found that in failing circulation due to cardiac disease there is an in-

creased amount of lactic acid present in the resting blood, and that this is in proportion to the degree of circulatory failure. It is, however, kept within reasonable limits but with each acute exacerbation of circulatory failure the lactic acid mounts in a very pronounced manner. But this cannot be tolerated for long; if it is not corrected within a short time cardiac function ceases. This is what probably happens in all cases of either acute or chronic heart failure. It must be appreciated that the accumulation of lactic acid in the circulating blood is but a reflection of what is occurring in the muscles, and as it has been shown above that the myocardium is intolerant of local changes of pH and accumulation of lactic acid through oxygen want, it becomes quite clear as to the reason of cardiac arrest under such conditions. Through the associated pulmonary and circulatory functional defects it has been found that cases with failing compensation are unable to increase their oxygen intake beyond a certain point, which point is roughly in proportion to the degree of circulatory impairment. This has been confirmed by Eppinger, Kisch, and Schwartz, 1927,¹² and again in 1930 by Harrison and Pilcher.¹³

In conclusion, we may summarize that there are three important known conditions which may lead to failure of the cardiac muscle to function properly through a defect in cardiac glycogen metabolism. They are oxygen want, thyrotoxicosis and insulin deficiency.

REFERENCES

¹KILBOURN, L. G., and MACLEOD, J. J. R.
Observations on certain invertebrates and fishes, *Quart. Jr. Exper. Physiol.*, 1919-20, xii, 317-330.

²MACLEOD, J. J. R., and PRENDERGAST, D.
J. Glycogen in the heart and skeletal muscles in starved and well-fed animals, *Proc. Roy. Soc. Canada*, 1921, Sec. V, xv, 37-40.

- ³KATZ, L N , KERRIDGE, P T , and LONG, C N H Lactic acid in mammalian cardiac muscle—Part III Changes in the hydrogen-ion concentration, *Proc Roy Soc, Ser B*, 1925-26, xcix, 26-27
- ⁴BAYLISS, L E , MULLER, E A , and STARLING, E H The action of insulin and sugar on the respiratory quotient and metabolism of the heart-lung preparation, *Jr Physiol*, 1928, lxxv, 33-47
- ⁵EVANS, G T (In press)
- ⁶LAWRENCE, R D , and McCANCE, R A The effect of starvation, phloridzin, thyroid, adrenalin, insulin and pituitrin on the distribution of glycogen in the rat, *Biochem Jr*, 1931, xxv, 570-578
- ⁷LOVATT EVANS, C The gaseous metabolism of the heart and lungs, *Jr Physiol*, 1912, xlv, 213-234
- LOVATT EVANS, C , and HILL, A V The relation of length to tension development and heat production on contraction in muscle, *Jr Physiol*, 1914, xlix, 10-16
- LOVATT EVANS, C The mechanism of cardiac acceleration by warmth and by adrenalin, *Jr Physiol*, 1917, li, 91-104
- LOVATT EVANS, C The velocity factor in cardiac work, *Jr Physiol*, 1918, lii, 6-14
- ⁸STARLING, E H , and VISSCHER, M B The regulation of the energy output of the heart, *Jr Physiol*, 1926-27, lxxii, 260
- ⁹CRUICKSHANK, E W H , and SHRIVASTAVA, D L The action of insulin on the storage and utilization of sugar by the isolated normal and diabetic heart, *Am Jr Physiol*, 1930, xcii, 144-159
- ¹⁰KATZ, L N , and LONG, C N H Lactic acid in mammalian cardiac muscle—Part I The stimulation maximum, *Proc Roy Soc, Ser B*, 1925-26, xcix, 8-20
- ¹¹ANDRUS, E C , McEACHERN, D , PERLZWEIG, W A , and HERMAN, S Comparative sensitivity to oxygen want and to sodium lactate of the hearts of normal and thyroxinized animals, *Jr Clin Invest*, (Proc 22nd annual meeting), 1930-31, ix, 16-17
- ¹²EPPINGER, H , KISCH, F , and SCHWARZ, H Das Versagen des Kreislaufes, 1927, Berlin
- ¹³HARRISON, T R , and PILCHER, C Studies in congestive heart failure, III The respiratory exchange during and after exercise, *Jr Clin Invest*, 1929-30, viii, 291-315

Fatal Cinchophen Poisoning

Report of Six Cases

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IN a previous article we¹ reported four fatalities from the use of cinchophen. Three of the patients had been under a mail order treatment for chronic arthritis. All four cases exhibited subacute hepatic degeneration ("yellow atrophy"). Eleven similar cases studied at necropsy by others, presented analogous changes. Several cases subsequently reported, together with others that were overlooked in the preparation of the previous report, increase the total number of fatalities in the literature to thirty-two.¹⁻²⁰ Of this number twenty-six have been autopsied. In all of these cases the essential pathological changes were limited to the liver. Recently we have observed an alarming increase in the incidence of such cases in this vicinity. It is hoped that a report of such cases will call attention to the danger attending the use of cinchophen and its derivatives.

The clinical diagnosis of this entity following the appearance of jaundice is not difficult. The history usually reveals a female patient past middle age who has suffered from some arthritic

or neuritic condition of a chronic nature. Cinchophen or some proprietary "rheumatism cure" has been taken, following which the pain has been greatly relieved. After a short interval a progressive, painless jaundice appears associated with epigastric distress, pyrosis and vomiting. In the earlier stages a physical examination reveals a moderate jaundice and a slightly enlarged tender liver. As the disease progresses the liver gradually diminishes in size. Objective demonstration of the liver may be accomplished by an oxypertoneum procedure followed by a radiographic flat plate of the abdomen. In severe cases the patient may be comatose. Laboratory examinations may show albumin, casts and bile in the urine. Tyrosin and leucin crystals have been found in many of the severe cases. The icteric index is increased. The Van den Bergh test shows both a prompt positive and a delayed positive reaction. Frequently, a moderate secondary anemia is present.

REPORT OF CASES

Case I. Miss E. W., white, age 64, case no. 153-172, entered the Los Angeles General Hospital, April 4, 1931, on the service of Dr. B. S. Frary, and died June 21, 1931. In August, 1930, she had noticed some swelling of her finger joints and upon the advice of a neighbor began taking six tablets of "Ren-

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ton's Hydrocin" daily. She continued this dosage for several months. Each tablet contains approximately five grains of cinchophen.²¹ In December, 1930, she was deeply jaundiced and the liver dullness was markedly decreased. There was slight abdominal distention and edema of the legs. The stools were of normal color. She had never had pain in the region of the liver or gall bladder. The jaundice gradually diminished until admission to the hospital. The physical examination at that time revealed a well nourished white female very slightly jaundiced but with marked ascites and edema of the lower extremities. The superficial veins of the abdomen were distended.

Laboratory examinations gave the following data. The urine was negative except for occasional granular casts. No leucin or tyrosin crystals were found. The phenolsulphonphthalein dye excretion test showed 25 per cent function in one hour.

The study of the blood showed Hemoglobin, 81 per cent, erythrocytes, 3,940,000, color index, 1.03, leukocytes, 9,800, polymorphonuclear neutrophils, 74 per cent, with a slight shift to the left. The icterus index was 22. The Van den Bergh test was promptly positive (direct), while the indirect was 2.1. The blood chemical findings were normal on admission but on June 6, 1931, the total non-protein nitrogen had risen to 60 mgm per 100 cc of blood, although the preformed creatinine was 1.5 mgm per 100 cc of blood.

Numerous abdominal tapplings were done, each with the removal of several liters (7 to 8) of cloudy, straw-colored fluid. On one of these occasions, after the removal of 8000 cc of fluid, 9000 cc of oxygen were introduced and an X-ray plate made, which revealed a very small liver shadow.

Owing to intractable ascites and pyloric obstruction, an omentopexy and a posterior gastro-enterostomy were done on June 18. The pylorus was about the size of the little finger, probably the result of an old ulcer. The gall bladder was normal. The liver was much smaller than normal, irregular, hard, and had the granular appearance of cirrhosis. No section was removed for microscopic study. The post-operative course was stormy, much vomiting occurred, and death ensued

June 21, 1931. Postmortem examination was refused.

Case II R. B., a white male, aged 70, case no 165-539, was admitted to the Los Angeles General Hospital, June 26, 1931, on the service of Dr. J. M. Lacey, and died July 8, 1931. For several years he had suffered with "rheumatism" and began taking "Renton" tablets²¹ two months before admission. In all, about 45 were taken in the first month but none since. The only untoward effect he noticed was marked itching of the skin after the first thirty tablets. He felt greatly improved until three weeks before entrance at which time he noticed the appearance of a progressive jaundice associated with weakness, loss of weight, and tenderness over the liver.

The physical examination showed temperature, 98° F, pulse, 84, blood pressure, 130/64. The patient appeared well nourished and was deeply jaundiced. The area of liver dullness was decreased.

Laboratory examinations gave the following data. The urine showed four plus albumin but was otherwise negative. The Wassermann and Kahn reactions on the blood serum were negative. The erythrocytes numbered 4,450,000, the leukocytes 11,800, hemoglobin 80 per cent (Tallqvist). The blood chemistry was normal. The icterus index ranged from 143 on admission to 166 on July 3. The Van den Bergh test gave a prompt direct reaction and an indirect of 35.

Glucose was administered frequently intravenously in 10 per cent solution. The patient began vomiting after meals on July 3. He became comatose on July 7, and died on July 8, 1931. Permission for postmortem examination was refused.

Case III Mrs. V. D., a widow white, age 64, case no 166-678 entered the Los Angeles General Hospital July 4, 1931, on the service of Dr. F. W. Otto and died July 11, 1931. Following a fall ten years before, she had suffered with attacks of pain in the right side none of which were severe. She had never before been jaundiced. A week prior to admission jaundice was first observed. In March (1931) she had begun taking "Renton" tablets²¹ for "rheumatism" in her right knee. She stated she took twelve

tablets in all and that though they made her dizzy the "rheumatism" disappeared.

The physical examination revealed a somewhat stuporous, deeply jaundiced, rather obese woman. The temperature was 98° F; pulse, 80, respiration, 19, blood pressure, 142/72. The area of liver dullness was greatly decreased. No other abnormal findings were present.

The laboratory examination showed many tyrosin and leucin crystals, many pus cells and bile were found in the urine. The stool had a faintly yellow color. The icterus index was 200. The Van den Bergh test was promptly positive in the direct reaction and 25 in the indirect. The non-protein nitrogen was 54 mgm per 100 cc of blood, preformed creatinine, 17 mgm. The Wassermann and Kahn reactions on the blood serum were negative.

The patient gradually became comatose and died July 11, 1931. The *postmortem examination* was made by Dr J H Schaeffer, Assistant Coroner's Surgeon of Los Angeles County.

The liver was very small, about the size of two fists and weighed about 500 grams. The organ was firm and leathery, but not nodular. The capsule was pale, gray-green and finely wrinkled. The surface made by cutting appeared finely mottled, dark green and gray, somewhat resembling an obstructive biliary cirrhosis in the gross. The microscopic sections showed almost complete disappearance of the hepatic cells and replacement of the shrunken lobules by fibrous-appearing tissue. In some areas a more acute type of hepatic necrosis was present. The bile ducts were apparently increased in number and considerable round cell infiltration was present among them. The microscopic diagnosis was subacute hepatic degeneration. The common bile duct was almost completely stenosed at the ampulla but there was no distension above. The intestinal contents were faintly bile-stained. Many petechial hemorrhages were present over the pleura and pericardium.

Case IV J A G, a white male physician, age 56, was first seen by Dr J M Lacey on August 29, 1930 (case no 4072). During the preceding winter he had had an attack of pain in one foot and ankle, which

he believed to be rheumatism. He took Atophan for three or four weeks. This was followed by a severe generalized pruritis. This subsided, but marked jaundice developed, together with extreme weakness. Jaundice and weakness were present at the time of examination. He then had a rather severe anemia with a hemoglobin value of 29 per cent and an erythrocyte count of 2,350,000. A diagnosis of toxic hepatitis due to cinchophen was made. The jaundice subsided for a time and some improvement in health occurred. Severe jaundice recurred and he died February 15, 1931, with the physical findings of acute yellow atrophy of the liver. No *postmortem examination* was made.

Case V Mr D, a white male, age 62 years, was seen by Doctor Lacey in February, 1930. He had had neuritis in his legs and was given two tablets of Atophan three times a day for three weeks by his physician. Severe urticaria developed, followed by marked jaundice. The physical examination revealed extreme icterus. The liver was not palpable. There was no fever. A diagnosis of acute hepatic necrosis due to cinchophen was made. An intravenous solution of glucose was given. Small doses of insulin subcutaneously and alkalis by mouth were administered. He died on the same day. *Postmortem examination* was refused.

Case VI Mr J C, a white male, age 43 years, was seen by Dr Machlin on September 10, 1931, complaining of epigastric distress followed by vomiting. He had taken two hundred "Renton Hydrocin Tablets" during the preceding six months because of arthritis of the right hip. The total dose of cinchophen was hence one thousand grains.²¹

Examination revealed a well nourished man of forty-three years who was slightly jaundiced. The entire abdomen was tender but not rigid. The temperature was subnormal. The stools were clay colored. The remaining findings were not altered. A diet rich in carbohydrates was ordered. The jaundice became progressively deeper during the following forty-eight hours. He remained conscious until the time of his death on September 12, 1931.

At *autopsy* the body was extremely jaundiced. The thoracic viscera were icteric and showed multiple petechiae beneath the serosal

surfaces. The gastro-intestinal tract was negative. The liver weighed 780 grams. It was quite flabby and the capsule was slightly wrinkled. The cut surface was mottled with yellow, raised, hyperplastic areas alternating with depressed reddened areas. The bile ducts contained a clear, mucoid material. The microscopic sections showed an extensive necrosis of the polygonal cells with connective tissue replacement. There was a moderate periportal round cell infiltration. The hyperplastic areas showed swollen hepatic cells deeply stained with bile. Aside from a moderate cloudy swelling of the kidneys, the remaining viscera were normal. The cause of death was "cinchophen poisoning with subacute yellow atrophy of the liver."

SUMMARY

1 Six additional fatalities due to cinchophen are reported.

2 Four of the six cases resulted from the use of Renton's Hydrocin tablets, a mail-order remedy containing cinchophen.

3 The six cases conform to the typical clinical syndrome of this intoxication.

We are indebted to Drs. Lacey, Frary, Otto, Schaeffer, and Machlin for permission to publish their data.

REFERENCES

- ¹PARSONS, L., and HARDING, W. G. Cinchophen (Atophan) poisoning, report of four cases, *Am Jr Med Sci*, 1931, clxxx1, 115-125.
- ²CABOT, R. C. Case records of the Massachusetts General Hospital, case 11231, *Boston Med and Surg Jr*, 1925, cxci, 1122.
- ³WILLCOX, SIR W. H. Atophan derivatives in rheumatism, *Brit Med Jr*, 1926, 11, 273-274.
- ⁴WELLS, C. J. L. Atophan derivatives in rheumatism, *Brit Med Jr*, 1926, 11, 759.
- ⁵LANGDON-BROWN, W. Atophan derivatives in rheumatism a caution, *Brit Med Jr*, 1926, 11, 37.
- ⁶HITZENBERGER, K. Case report, *Wien klin Wchnschr*, 1927, xi, 205.
- ⁷SINGER, S. Case Report, *Wien klin Wchnschr*, 1927, xi, 238-239.
- ⁸RAKE, G. W. A case of subacute yellow atrophy following taking of Atophan, *Guy's Hosp Rep*, 1927, lxxvii, 229-237.
- ⁹LOEWENTHAL, L. J. A., MCKAY, W. A., and LOWE, E. C. Acute yellow atrophy of liver following administration of Atophan, *Brit Med Jr*, 1928, 1, 592-593.
- ¹⁰SUTTON, D. C. Acute yellow atrophy of liver following taking of cinchophen, *Jr Am Med Assoc*, 1928, xci, 310-312.
- ¹¹WEIL, P. Leberatrophie nach Atophanbehandlung? Ein Obergutachten, *Med Welt*, 1928, 11, 257-259.
- ¹²LONDON LETTER. *Jr Med Assoc*, 1928, xc, 1229.
- ¹³McVICAR, C. S., and WEIR, J. F. Acute yellow atrophy possibly due to poisoning by Atophan. *Med Clin No America*, 1929, xii, 1526-1528.
- ¹⁴REICHLE, H. S. Toxic cirrhosis of liver due to cinchophen, *Arch Int. Med*, 1929, xlv, 281-288.
- ¹⁵ANDERSON, S. D., and TETER, D. P. Acute yellow atrophy of the liver following administration of oxyl iodide, *Jr Am Med Assoc*, 1929, xciii, 93.
- ¹⁶STACY, L. J., and VANZANT, F. R. Poisoning from cinchophen, *Minnesota Med*, 1930, xiii, 327-328.
- ¹⁷RABINOWITZ, M. A. Atrophy of the liver due to cinchophen preparations. *Jr Am Med Assoc*, 1930, xcvi, 1228-1233.
- ¹⁸WALKER, W. G. Cinchophen and acute yellow atrophy of the liver, *New England Jr Med*, 1931, cciv, 253-254.
- ¹⁹BEAVER, D. C., and ROBERTSON, H. E. The specific character of toxic cirrhosis observed in cinchophen poisoning, a review of five fatal cases, *Am Jr Path*, 1931, vii, 237-258.
- ²⁰BOGEN, E. Cinchophen poisoning, report of case, *Cal and Western Med*, 1931, xxxv, 269.
- ²¹BUREAU OF INVESTIGATION. Renton's Hydrocin tablets, *Jr Am Med Assoc*, 1931, xcvi, 209-210.

Agranulocytic Angina—Report of a Case

With Bacteriological Study

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SINCE Schultz¹ in 1922 reported a peculiar type of necrosing angina with marked absolute and especially granulocytic leucopenia, there have been increasing numbers of these cases described in the medical literature. To this condition Schultz gave the name of agranulocytosis. Later Friedemann² changed this designation to agranulocytic angina. It would seem that Schultz's original terminology is the more fitting. We feel that a disease of such marked virulence deserves our closest study. It is for this reason we wish to report our case in detail. The case is as follows:

Mrs. H. C. A. (seen with Drs. P. V. Ledbetter and M. H. Mohle), white, American, aged 35, entered the Baptist Hospital, September 23, 1930, complaining of extreme restlessness, weakness and a severe infection of the mouth. On the day previously she had developed a sore mouth, followed by ulcerations on the hard palate and between the upper central incisors, high temperature, chilly sensations and weakness.

The previous history was negative with the exception of frequent attacks of sore throat for several years previously and glycosuria for the past year. Records of blood pressure systolic, 140, diastolic, 90, showed no abnormalities.

Examination revealed a well developed woman, 35 years of age, 5 feet, 6 inches tall, weighing approximately 155 pounds, blood pressure systolic, 140, diastolic, 90,

temperature 102° F., pulse, 100, respiration 22. She was very restless and prostrated. The physical examination was negative, except for marked reddening, swelling and small ulcerations on the hard palate, associated with considerable swelling and redness of the gums. The submaxillary and lateral cervical glands were swollen and slightly tender.

Blood examination showed leucocytes, 3,700; small lymphocytes, 70 per cent, large lymphocytes, 10 per cent, polymorpho-neutrophils, 9 per cent, eosinophils, 1 per cent, erythrocytes, 3,900,000, hemoglobin, 75 per cent; no abnormal red cells. Smears from the mouth showed Vincent's organisms. Urinalysis revealed a small amount of sugar. The blood Wassermann reaction was negative. A blood culture was negative. Blood chemistry normal. Bleeding time was 2 minutes, coagulation time, 5 minutes, and platelet count, 110,000. From this time onward the necrosis in the mouth advanced rapidly until the left upper alveolar process and the soft and hard palate were completely necrosed. During this period there appeared on the flexor surface of the right forearm, the anterior surfaces of the legs (figure 1) and the right malar area of the face, black areas, which resembled a dry leathery necrosis. The areas on the arms and legs extended rapidly, the one on the face slightly. Later they began to regress at the edges, leaving a rounded, irregular border. At no time was any suppuration nor pain noted. The temperature ranged from 101° to 105° F., and the pulse from 120 to 140 during the first 24 days. From her entrance to the hospital until October 17 she had received six blood transfusions without any improvement. On the evening of

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October 17, we began giving her daily 120 grams of raw fetal spleen in tomato juice, the following morning her total leucocytes were 1500, polymorphoneutrophils, 28 per cent, small lymphocytes, 63 per cent, large lymphocytes, 9 per cent, and the temperature was ranging from 103° to 105° F. Four days after beginning the fetal spleen the temperature had dropped to 100° F and leucocyte count was now 8000 with 80 per cent polymorphoneutrophils, 10 per cent small lymphocytes and 10 per cent large

became worse and her leucocyte count on the second day thereafter was 2700 with 53 per cent polymorphoneutrophils, which fell to 19 per cent by the seventh day. On the sixth day (Nov 16) it was decided to increase the fetal spleen to 180 grams per day. The leucocytes began to increase rapidly until by November 21 the count was 9000 with polymorphoneutrophils, 73 per cent. On this date she had a severe hemorrhage from the left external maxillary artery, which had been eroded by the



FIG 1 Areas of black, leathery consistency, extending into the deeper layers of the skin, borders rounded and irregular, regression centripetally, leaving dark pinkish margins which faded entirely as areas became smaller

lymphocytes. By referring to figures 2 and 3, further understanding of the progress will be facilitated. It will be noted that the clinical and hematological evidences of recovery were considerable until on November 10 it was decided to remove the extensive necrotic material from the mouth. At this time the patient was tremendously improved and gaining strength rapidly, the temperature was 99° F, total leucocyte count, 4000, polymorphoneutrophils, 63 per cent, small lymphocytes, 32 per cent, and large lymphocytes, 5 per cent. Following the removal of the necrotic tissue she rapidly

extensive necrosis in the mouth, and death seemed imminent for several hours. The necrosed area was tightly packed, and she rallied somewhat. On November 23 a blood transfusion was given. Considerable bleeding continued around the packing, and on November 29, another large hemorrhage occurred. Another blood transfusion was given, and the left external carotid artery was ligated. The bleeding stopped immediately but the patient died the next day. Following this last hemorrhage the total leucocyte count and the polymorphonuclear neutrophils increased until on the day of her

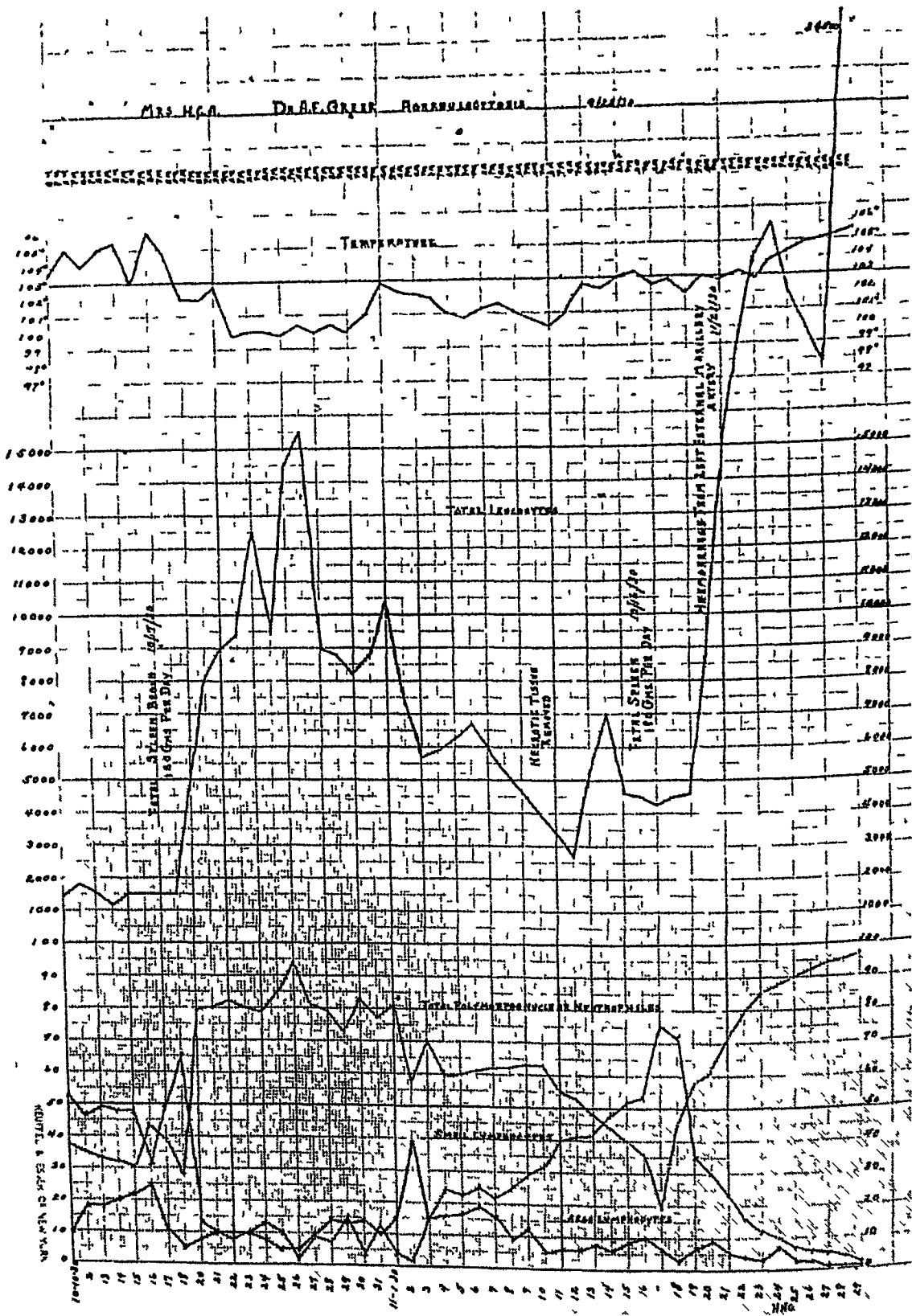


FIG 2 Progress of patient, showing temperature curve and hematological aspects Note reaction following exhibition of fetal spleen

death they were 34,500 and 97 per cent respectively. Such a count is the usual finding following severe hemorrhages. However, it is not an accurate appraisal of the total corpuscular content of the body because of the extreme fluid loss from the hemorrhage. But as we have heretofore outlined, the well marked leucocytic response to the increased fetal spleen intake took place before the hemorrhage occurred. Autopsy was declined.

EXPERIMENTAL INVESTIGATION

On October 20, 1930, three guinea pigs were injected intraperitoneally with 5 cc,

3 cc, and 25 cc, respectively, of Mrs H C A's blood. Two of the pigs were unaffected, but one died on the eighth day thereafter. The following table shows its blood reaction.

At autopsy of this animal nothing unusual was noted except that at the site of the injection on the abdomen there was an area about an inch in diameter of dark necrosis, which was identically similar to the areas on the patient's arms, legs and face. No changes were noted in the internal organs macroscopically. A culture was obtained from the heart's blood and we obtained three types of organisms. (1) Many gram-nega-

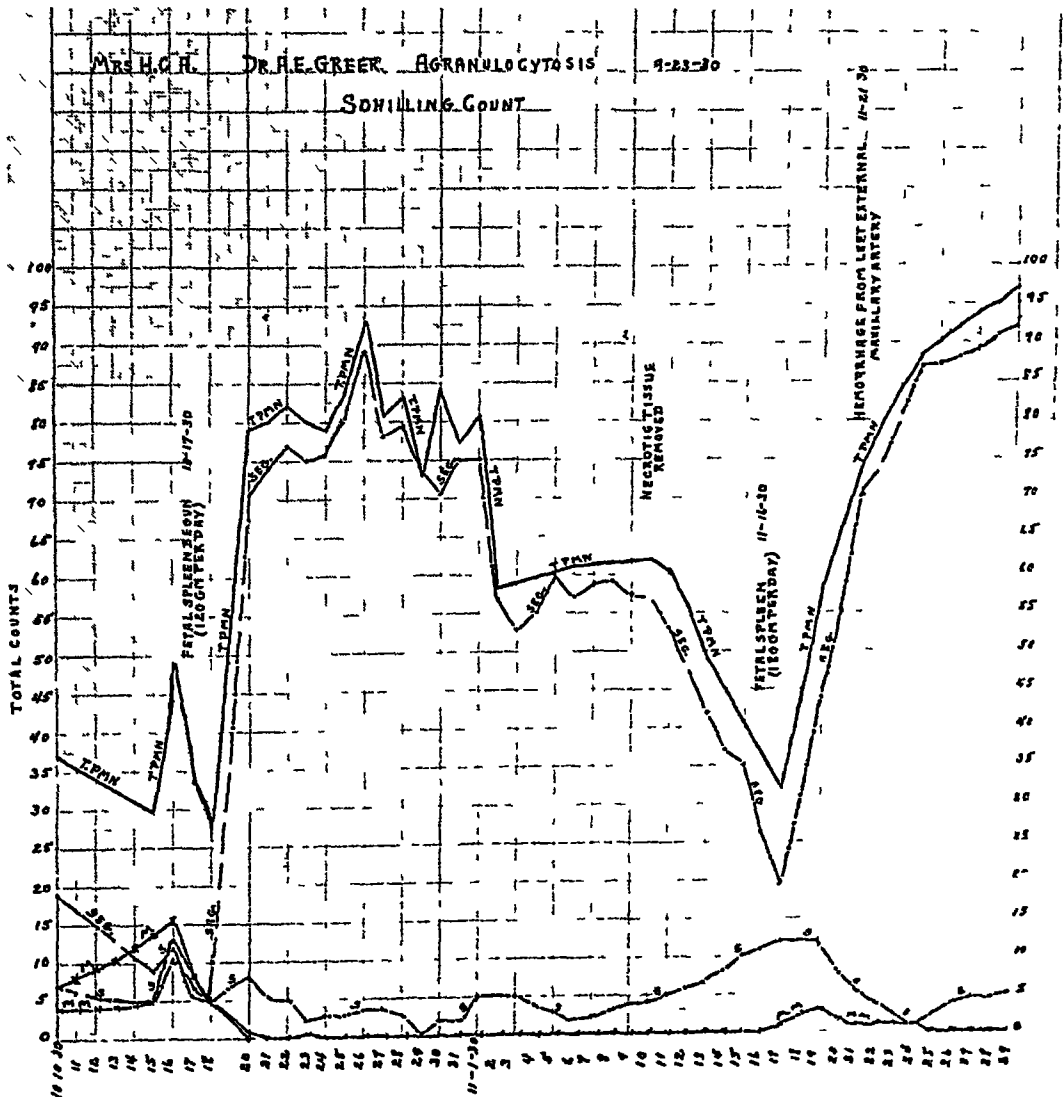


FIG 3 Illustrating polymorphoneutrophil trend of Schilling count

GUINEA PIG 1

DATE	WBC	SL	L.L.	POLYS.	LOS	BASO	TRANS	REMARKS
10/20/30	12,400	74	4	20	2	0	0	
10/21/30	9,650	38	6	54	2	0	0	
10/22/30	15,250	31	6	59	2	0	2	
10/23/30	10,150	52	5	43	0	0	2	
10/24/30	21,400	25	4	65	4	0	2	A dark area ap- pearing at the site of the injection like the area on patient's legs
10/25/30	13,700	60	5	33	0	1	1	
10/27/30	8,600	72	0	28	0	0	0	
10/28/30	3,800	80	8	10	0	0	2	Pig died This count was made at death

tive bacilli, (2) few gram-negative diplo-
cocci, (3) few gram-positive diplococci
We were successful in isolating the gram-
negative bacillus and also the gram-negative
diplococcus The gram-negative bacillus
hereafter will be referred to as bacillus 1A
(figure 4) But we were unable to secure
a pure culture of the gram-positive diplo-
coccus, which died out on frequent trans-
plantations The cultural characteristics of
these organisms may be found on charts I
and II

On October 23, 1930, two rabbits were
inoculated intravenously with 2 cc and 25
cc, respectively, of citrated blood from Mrs
HCA Two uninoculated rabbits were
used as controls. Blood counts were made
on these rabbits from October 23, 1930,
through November 5, 1930, and no changes
were observed

On November 6, 1930, blood counts were
made on three guinea pigs previous to the
intrapertitoneal inoculation of each one with
0.5 cc of a 24 hour broth culture of the

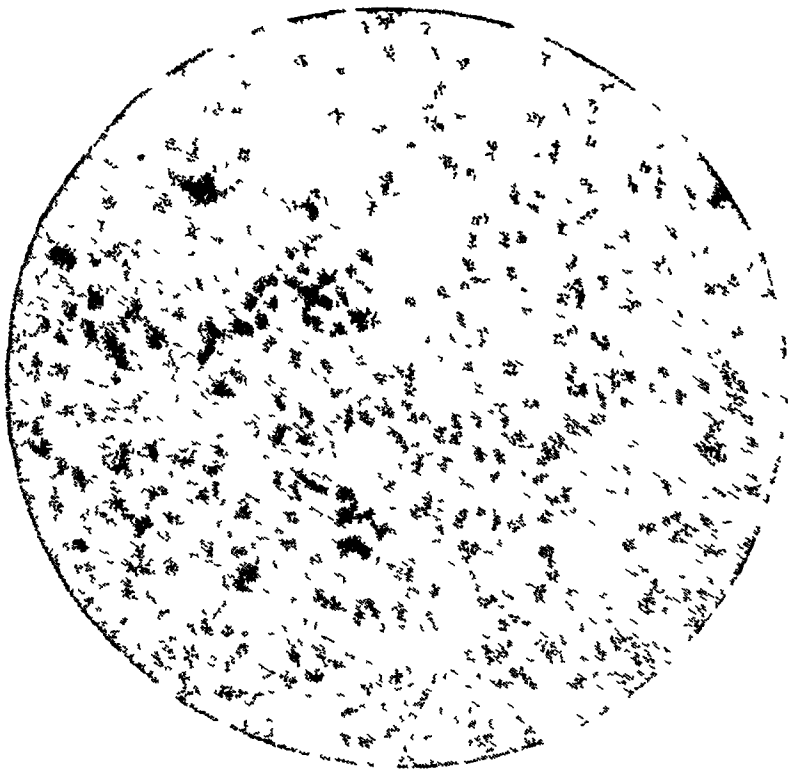


FIG 4 Gram-negative, motile Bacillus 1A, obtained from the heart blood of guinea pig No. 1, which had been inoculated with patient's blood

different organisms recovered. Counts were made at the end of 6 and 24 hours and then every 24 hours for 6 days after the inoculation. Little change was noted in these counts which will be found below.

negative diplococci, a few gram-positive diplococci, and a few spirilla. By transfer and isolation a pure culture of gram-negative bacillus (to be referred to as *Bacillus* 1B) (see figure 5) was secured.

GUINEA FIG 4

0.5 cc of Broth Culture of Gram-Negative and Gram-Positive Diplococci Intraperitoneally

DATE NOV 1930	RBC.	WBC	HEMO (M)	NEUTROPHILS (MM S SEG)	SL	LL	MONO-EO CYTES	BAS	TEMP	TIME OF DAY
6	4,752,000-8,000		90%		12	86	2		102.6	11 A M
7	4,736,000-8,200		90%		23	75			103.4	10 A M
7	4,992,000-5,000		90%	1	45	50	4		103.6	4 P M
8	4,768,000-7,000		90%	1	30	59	6		103	10 A M
9	4,704,000-6,000		90%		20	77	3		103.6	10 A M
10	4,490,000-8,400		90%		22	75	2	1	102.6	10 A M
12	4,080,000-8,000		90%		15	85				
Pig unaffected										

GUINEA FIG 5

0.5 cc of Broth Culture of Gram-Negative Bacilli 1A Intraperitoneally

DATE NOV 1930	RBC	WBC	HEMO (M)	NEUTROPHILS (MM S SEG)	SL	LL	MONO-EO CYTES	BAS	TEMP	TIME OF DAY
6	4,752,000-8,000		90%		58	42			102	11 A M
7	4,630,000-9,200		90%		67	30	3		102.6	10 A M
7	4,800,000-5,800		90%	1	54	40	5		103.6	4 P M
8	4,880,000-7,200		90%		22	74	4		102.6	10 A M
9	4,912,000-7,000		90%		28	68	2	2	103	10 A M
10	4,450,000-10,000		90%		47	51	2		102.6	10 A M
12	4,230,000-9,400		90%		35	62	3		102.2	10 A M
DEC 1	Pig found dead. Autopsy. Cultures made from heart blood.									

GUINEA FIG 6

0.5 cc of Broth Culture of Gram-Negative Bacilli and Gram-Positive and Gram-Negative Diplococci Intraperitoneally

DATE NOV 1930	TIME OF DAY	RBC	WBC	HEMO (M)	NEUTROPHILS (MM S SEG)	SL	LL	MONO-FO CYTES	BAS	TEMP
6	11 A M	5,008,000-8,800		90%		50	48	2		101
7	10 A M	5,040,000-10,000		90%		58	38	1	2	101.6
7	4 P M	5,040,000-5,200		90%		78	21	1		102
8	10 A M	4,884,000-7,800		90%	2	54	44			100.8
9	10 A M	4,976,000-9,200		90%		64	35	1		101.4
10	10 A M	4,710,000-9,800		90%		26	70	2	1	101.2
12	10 A M	4,570,000-8,400		90%	1	25	70	1	2	100.6
Pig Unaffected										

On November 12, 1930, direct smears and cultures were made from the necrotic tissue which had been removed from the patient's mouth. These showed many gram-negative bacilli, moderate numbers of gram-

On November 17 we injected intraperitoneally three guinea pigs with different organisms from the original culture. This was a repetition of work done on guinea pigs 4, 5 and 6 and we hoped to get more

CHART I
Cultural Characteristics and Staining Reactions

	NAME OF ORGANISM	INDOL	MOTILITY	SIZE	GELATIN CLUSTERS	ARRANGEMENT	ON COOD AGAR
Bac 1A	Gram negative bacillus from original culture from Baptist Hospital, (guinea pig 1)	Formation sl 1 plus at end of 8th day	Actively motile	1.5 to 2 microns by 5 micron	Clusters ends round	Growth best at top, sl liquefaction at end of 5th day	Spreading growth, decided odor, opaque, brown at streaks, yellow-green at edges
Bac 1B	Gram negative bacillus from necrotic area of mouth	Negative at end of 8th day	Actively motile	1.2 microns to 2 microns by 5 micron	Clusters ends round	Growth best at top, sl liquefaction at end of 5th day	Spreading growth, decided odor, opaque, complete discoloration
Bac 1C	Gram negative bacillus from guinea pig 5, which died after injection of Bac 1A	Sl 1 plus at end of 8th day	Actively motile	1.5 to 2 microns by 5 micron	Clusters ends round	Uniform, very sl liquefaction at end of 5th day	Spreading growth, no odor, sl opaque brown at centers, yellow-green at edges
B 2	Gram negative and gram positive diplococci from original culture from Baptist hospital, (guinea pig 1)	Positive in 3 days	Actively motile	Gram negative 5 microns by 4 micron Gram positive 1.5 microns by 7.5 micron	Round gram negative in clusters, Gram positive scattered	Growth slow no liquefaction	Spreading yellow pigment, slight odor, slight discoloration
B 3	Gram negative diplococci isolated from B 2 (guinea pig 1)	Positive in 3 days	Actively motile	5 microns by 4 micron	Clusters	Growth slow Slight liquefaction	Confined to streaks, no odor, slight discoloration
B 4	Gram negative diplococci recovered from heart blood of guinea pig 9 inoculated with B 2	Negative in 3 days	Actively motile	5 microns by 4 micron	Clusters	Growth slow Slight liquefaction	Confined to streaks no odor, slight discoloration

CHART I
Cultural Characteristics and Staining Reactions

POTATO MEDIA	NUTRITION BROTH	ENDO-AGAR	RELATION TO OXYGEN	SPORE STAINING	CAPSULE STAINING
Spreading growth, decided odor, media light brown to dark brown	Surface growth, flocculent, turbid, no odor, abundant sediment	Many pink colonies	Facultatively aerobic	24 hr culture heated to 80° C, transferred to agar slant No growth Acid-fast method No spores	Gram's—No capsules noted India Ink—No capsules noted
Spreading growth, decided odor, media dirty brown	Surface growth, flocculent, turbid, no odor, moderate sediment	Many pink colonies, few white colonies	Aerobic	24 hr culture heated to 80° C, transferred to agar slant No growth Acid-fast method No spores	Gram's—No capsules noted India Ink—No capsules noted
Spreading growth, little odor, media light to dark brown with reddish areas	Surface growth, flocculent, no odor, mod sediment	Many pink colonies	Aerobic	24 hr culture heated to 80° C, transferred to agar slant No growth Acid-fast method No spores	Gram's—No capsules noted India Ink—No capsules noted
Spreading growth, slight odor, dark brown	Surface growth, flocculent, no odor, mod sediment	Mod pink colonies	Aerobic	24 hr culture heated to 80° C, transferred to agar slant Acid-fast method No spores	Gram's—No capsules noted India Ink—No capsules noted
Scanty growth but slightly spreading medium	Scant-surface growth, no odor, mod sediment	Mod pink colonies	Aerobic	24 hr culture heated to 80° C, transferred to agar slant No growth Acid-fast method No spores	Gram's—No capsules noted India Ink—No capsules noted
Slightly spreading, brown with dark reddish areas	Scant-surface growth, no odor, mod sediment	Mod pink colonies	Aerobic	24 hr culture heated to 80° C, transferred to agar slant No growth Acid-fast method No spores	Gram's—No capsules noted India Ink—No capsules noted

CHART II
Fermentation Reactions

ORGANISM	DEXTROSE	LACTOSE	SACCHAROSE	MALTOSE	MANNITE	LEVULOSE	LITMUS	DULCITE	RAFFINOSE	TREHALOSE	RHAMNIT	XYLOSE	INOSIT	ARABINOS
Bac 1A Gram negative bacillus	AG 17%	AG 25%	AG 16%	AG 16%	AG 18%	AG 12%	Acid Milk coagulated	G 5%	G 33%	G 10%	G 30%	G 2%	AG 2%	G 20%
Bac 1B Gram negative bacillus	AG 2%	AG 17%	O	AG 13%	AG 26%	A No gas	Acid Milk coagulated	G 3%	G 20%	G	G 10%	G 45%	G 10%	G 15%
Bac 1C Gram negative bacillus	AG 3%	AG 2%	A No gas	AG 12%	AG 5%	AG 2%	Acid Milk coagulated	G 3%	G 28%	G 1%	G 2%	G 3%	G 3%	G 4%
Bact 2 Gram negative and positive diplococci	AG 14%	AG 21%	AG 30%	AG 17%	AG 30%	AG 18%	Acid (In 24 hrs) Incomplete coagulation	X	X	X	X	X	X	X
Bact 3 Gram negative diplococcus	A No gas	O	AG 2%	AG 10%	AG 1%	A No gas	Acid (In 24 hrs) Incomplete coagulation	X	X	X	X	X	X	X
Bact 4 Gram negative diplococcus	AG 3%	O	AG 4%	AG 1%	AG 3%	AG 3%	Acid (In 24 hrs) no coagulation	A	X	X	X	X	X	X
Bac Coli Communis	AG	AG	O	AG	AG		Acid Coag	+	+	AG	AG	+	O	AG
Bac Coli Communion	AG	AG	AG	AG	AG		Acid Coag	+	AG	AG	AG	AG	O	AG

Legend
AG=Acid and Gas
+ =Variable
O=No Acid nor Gas produced
A=Acid
G=Gas
X=Not tested
%=Refers to gas only

definite changes in the blood counts. Counts were made daily for 10 days and no changes were observed. However, we obtained a pure culture of gram-negative diplococci from the heart blood of guinea pig 9, which had been inoculated with the culture of gram-negative diplococci and gram positive diplococci.

On November 19, 1930, a guinea pig was injected intraperitoneally with 2 cc of broth culture of gram-negative *Bacillus* 1B.

On November 28, 1930, an effort to secure a pure culture of the gram-positive diplococci from the original culture was made by inoculating guinea pig 11 with 2 cc of broth

culture of gram-positive and gram-negative diplococci (with gram-positive diplococci predominating). On the next day, November 29, 1930, to lower the resistance of the guinea pig, 900 milliamperes seconds of x-ray exposure were given at cone distance and without filter. On the next day the same amount of exposure was given, and following the exposure, 3 cc of a broth culture of gram-positive and gram-negative diplococci were given intraperitoneally. On December 3, 1930, the guinea pig appeared very sick and during the day had an occasional convulsion. Two other exposures of x-ray of same amount were given on December 6

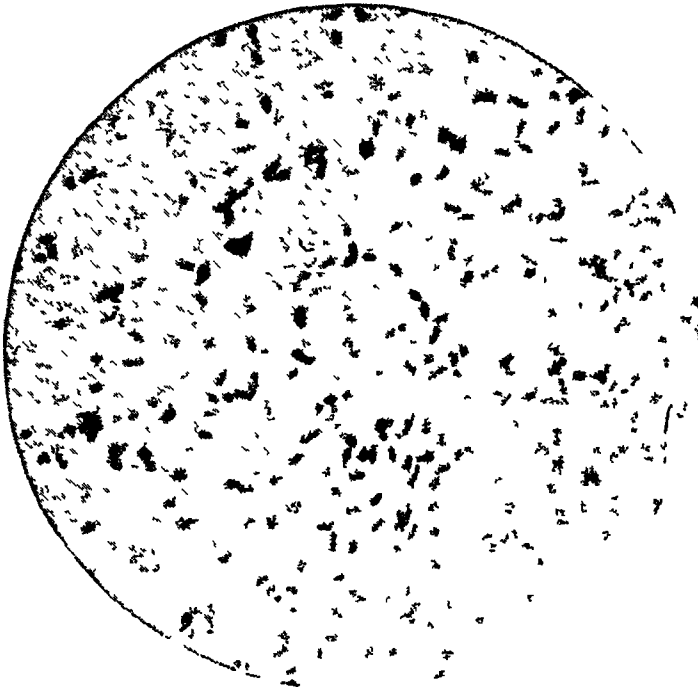


FIG 5 Gram-negative, motile *Bacillus* 1B, obtained by culture from necrotic tissue in patient's mouth

GUINEA FIG 10

DATE NOV 1930	TIME OF DAY	RBC	WBC	HEMO (M)	NEUTROPHILS (M) (S) (SEG)	SL	LL	MONO- CYTES	LO	BAS	TIP
19	4 P M	4,760,000	6,000	90%		25	75				103.4
20	10 A M	4,840,000	7,600	90%		31	67	2			102.8
21	10 A M	4,640,000	5,000	90%		20	80				101.0
22	10 A M	4,680,000	5,000	90%	1	18	79	2			100.8
24	10 A M	4,758,000	5,600	90%		19	77	4			101.8
25	10 A M	4,830,000	5,400	90%		17	71	12			100.6
26	10 A M	4,520,000	6,000	90%		10	89	1			101.2

GUINIA FIG 11
Gram-Negative and Gram-Positive Diplococci and X-Ray Exposure

DATE		TIME	RBC.	WBC	Hemo	Neutrophils	S.L.	L.L.	MONO-	FOBAS	TEMP
NOV		OF			(M	MM S SIG)			CYTES		
1930		DAY									
28	10	A M	4,960,000	9,400	90%		20	77	3		101.4
29	10	A M	4,736,000	19,200	90%		42	57	1		101.4
DEC											
1	10	A M	4,220,000	6,000	85%		17	82	1		101
2	10	A M	4,236,000	5,400	85%		16	83	1		100
3	10	A M	3,800,000	3,150	80%	2	25	72	1		104.4
4	10	A M	2,770,000	1,000	70%	3	76	20	1		103
5	10	A M	2,316,000	5,000	57.2%	7	20	70	2	1	103
6	10	A M	2,352,000	4,400	54.5%	3	38	58		1	102.8
8	10	A M	2,720,000	4,200	57.5%	2	63	33	2		102.8
9	10	A M	2,408,000	4,400	57.2%	4	58	37	1		102.2

and December 8, 1930 Discontinued counts after December 9, 1930 Guinea pig recovered

On the morning of December 1, 1930, guinea pig 5, which had been inoculated with 0.5 cc of broth culture of gram-negative bacillus 1A on November 6, 1930, was found dead Results of autopsy were as follows

Considerable peritoneal congestion and redness were noted with a moderate amount of free fluid in the peritoneal cavity There was moderate injection of the small intestines Kidneys externally were slightly injected Liver was very noticeably injected and red, almost nutmeg in appearance Gall bladder was distended and did not empty readily Cultures were taken from the peritoneal fluid and from the distended gall bladder The stomach was normal The spleen was dark red and slightly swollen Pancreas was normal The heart was normal The lobe of the left lung was hard, dark, and hemorrhagic In the right lung there was more extensive and scattered involvement, similar to that noticed on the left side, with some pleural ecchymosis Cut section of the lungs showed a moderate amount of air with clear, light yellow fluid exuding on pressure, as well as considerable amount of bloody fluid

From the heart's blood a pure culture of a gram-negative bacillus was recovered which we will hereafter refer to as Bacillus 1C (See figure 6) The peritoneal fluid and gall bladder were sterile

During the remainder of December we alternately transferred our organisms 1A,

1B, 1C, 2, 3 and 4 on dextrose broth for three days and agar three days We were able to keep luxuriant growths of the gram-negative bacilli 1A, 1B and 1C The diplococci 2, 3 and 4 grew less abundantly In an effort to revivify the organisms we planted each of these on dextrose broth for three days, transferred to gelatin for three days and then to agar slants The bacilli 1A, 1B, 1C, seemed to have been benefitted by the process while the diplococci were not

Guinea pig 12 was inoculated intraperitoneally on January 7, 1931, with 1/2 agar slant of the gram-negative Bacillus 1C A preliminary blood count showed red blood cells, 4,800,000, white blood cells, 8,800, small lymphocytes, 91 per cent, neutrophils, segmented, 9 per cent Another blood count was made on January 8, 1931, at 4.45 P.M. and showed red blood cells, 4,740,000, white blood cells, 4,800, small lymphocytes, 78 per cent, large lymphocytes, 1 per cent, neutrophils—segmented, 20 per cent, and stabs, 1 per cent The guinea pig was found dead early the next morning and the necropsy findings were as follows

Esophagus and trachea negative Pleural cavity contained about 0.5 cc of blood-tinged fluid There was a small ecchymotic area over the left parietal pleura The peritoneum was slightly injected The entire liver surface was covered with a white gelatinous material, and on the inferior surface of the right lobe was a large blotchy grayish-white area The internal surface of the liver was of normal color and consistency The spleen was negative The

stomach negative. On the inferior medial surface of the left kidney was a blotchy area of the same color as that on the liver, approximately 0.5 by 2 cms in diameter. Large and small intestines were negative. The peritoneal cavity contained about 10 cc of blood-tinged fluid. Culture from the heart blood revealed a gram-negative motile bacillus identical with 1C.

Guinea pig 13 was inoculated intraperi-

The peritoneal cavity contained about 15 cc of blood-tinged fluid. There was a small blotchy area on the external surface of the right lobe of the liver. The pancreas and spleen were negative. Kidneys negative. Multiple ulcers in the mucosa of the greater curvature of the stomach. Small intestine negative. Large intestine negative except for a perforation about 1 by 1.5 cms. There were about 5 cc of serofibrinous blood-

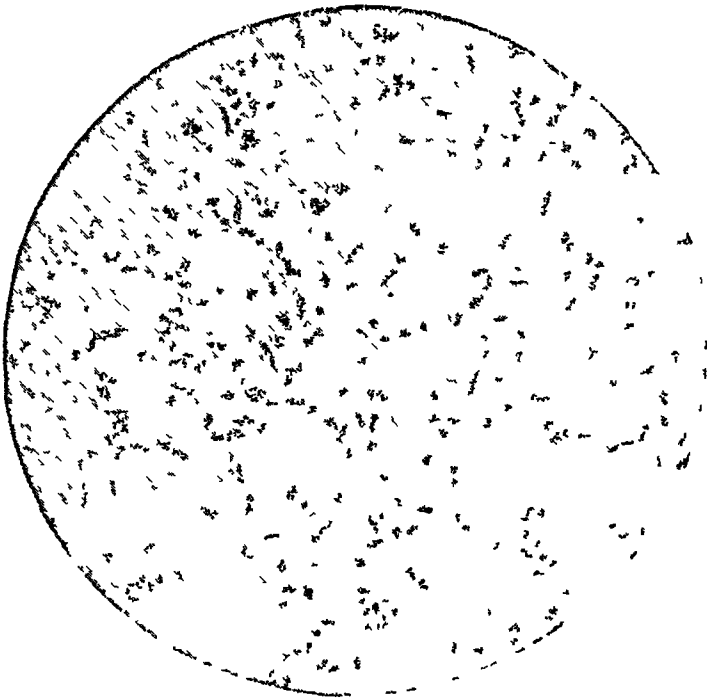


FIG 6 Gram-negative, motile *Bacillus* 1C, obtained from the heart blood of guinea pig No 5, which had been inoculated with gram-negative *Bacillus* 1A.

toneally on January 7, 1931, with one agar slant of the gram-negative *Bacillus* 1C. A preliminary blood count on January 7, 1931, showed red blood cells, 4,810,000; white blood cells, 6,800; small lymphocytes, 96 per cent; large lymphocytes, 1 per cent; neutrophils—stabs, 2 per cent; and segmented, 1 per cent. On January 8, 1931, at 4:45 P.M., another blood count showed red blood cells, 4,670,000; white blood cells, 3,800; small lymphocytes, 61 per cent; neutrophils—segmented, 38 per cent; and stabs, 1 per cent. The pig was found dead on the morning of January 9, 1931, and the following findings at autopsy were found:

tinged fluid in the pleural cavity. Both lungs were negative except for a rather marked degree of paleness. Trachea and esophagus were negative. Bacilli 1C obtained by culture from the heart blood.

Guinea pig 14 was inoculated intraperitoneally on January 7, 1931, at 9 P.M., with two slants of the gram-negative *Bacillus* 1C. A preliminary blood count showed red blood cells, 4,608,000; white blood cells, 6,200; small lymphocytes, 80 per cent; large lymphocytes, 2 per cent; neutrophils—segmented, 8 per cent; and stabs, 1 per cent. Another blood count made at 4:45 P.M. on January 8, 1931, showed red blood cells

GUINEA PIG 17

DATE JAN. 1931	TIME OF DAY	W B C	NEUTROPHILS (M MM S SEG)				S L	L L	MONO- CYTES	EOS	BASO
9	(Prelim)	11,800				13		86			1
10	(Prelim)	8,400			2	20		71	7		
12	10 A M	8,800				10		90			
12	12 Noon	6,700			2	46		49	3		
12	2 P M	3,450			11	34		55			
12	4 P M	3,650			15	14		66	5		
12	6 P M	2,700			15	12		73			
12	8 P M	0,950			10	15		70	5		
12	10 P M	0,750			13	23		58	5		1

(Platelets 210,000)

Guinea pig died during night of Jan 12, 1931

injected There was a moderate amount of subserous injection on the most dependent portion of the stomach The gastric submucosa showed a rather diffuse petechial and hyperemic injection in the most dependent area The liver was covered with a grayish-white exudate and there were scattered, discrete, slightly injected areas over both dorsal and ventral surfaces The pancreas was markedly injected and hemorrhagic The spleen was normal In the lung were small hemorrhagic areas scattered throughout The pleural cavity contained a small amount of hemorrhagic fluid

Guinea pig 16 Abdomen was filled with serosanguineous fluid There was a small perforation in the large bowel The large and small intestines were markedly injected with patchy diffuse hemorrhagic areas throughout On the superior and inferior surfaces of the liver were small scattered grayish-white and hyperemic areas The stomach showed marked subserous injection, the mucosa was markedly injected with diffusely scattered hemorrhagic areas The right kidney revealed a few scattered hemorrhagic areas on the medial surface There

was a small amount of blood-tinged fluid in the pleura Throughout both lungs were many hemorrhagic areas The entire surfaces of spleen and pancreas markedly injected

Guinea pig 17 Dead in approximately 36 hours after injection Grossly Sero-fibrinous exudate in peritoneal cavity, hyperemia in omentum and over greater curvature of stomach Very little inflammatory reaction elsewhere No petechiae Brain negative Chest two or three small hemorrhagic foci in lungs, none in pleura A very small amount of blood-tinged fluid was found in left pleural cavity All other organs negative Lymph nodes normal in abdomen and other parts Microscopically Peritoneal exudate almost entirely composed of bacteria, a very few polynuclear leucocytes were present in fibrin Lungs A few small hemorrhages, no inflammatory reaction Kidneys normal Spleen normal Liver slight edema of the surface from the proximity of the peritoneal inflammation Otherwise negative.

On January 15, 1931, a preliminary count was made on guinea pig 18 This was inocu-

GUINEA PIG 18

DATE JAN 1931	TIME OF DAY	W B C	NEUTROPHILS (M MM S SEG)				S L	L L	MONO- CYTES	EOS	BASO	TFMP
15	9 30 A M	9,400				15	77	7		1		1028
	(Prelim)											
15	4 15 P M	3,600			18	26	54	2				
16	9 00 A M	3,250			9	28	61	1	1			
17	9 30 A M	2,000				1	94	5				018
17	12 30 P M	1,250				2	97	1				016

Guinea pig died at 12 45 P M

lated intraperitoneally with ¼ slant of the gram-negative Bacillus 1C. Counts were made twice daily until death.

At autopsy a small amount of fluid and considerable fibrin were found in the peritoneal cavity. Omentum showed inflammatory thickening. All organs normal except for the slight, superficial inflammatory reaction of the peritoneal surfaces of the liver, stomach, and intestines. No petechiae. Microscopically Lungs normal. Kidneys normal. Liver Edema of superficial portions associated with the peritoneal inflammation, otherwise hepatic tissue was normal. The capsule showed swelling of the endothelium and fibrinous exudate infiltrated sparsely with leucocytes. At intervals there were collections of pyknotic nuclei close together, some lymphocytic, but most apparently the nuclei of degenerated, polynuclear leucocytes. Spleen normal. Omentum hemorrhage into the fat cells and between them. Inflammatory reaction was similar to that described on the liver capsule. There were a smaller number of polynuclears, and a greater proportion of plasma and lymph cell types, than would be expected in such an acute process. No true pus.

Guinea pig 19 was inoculated on January 27, 1931, with ½ slant of the gram-negative Bacillus 1C which had previously been revived. A preliminary count was made and another shortly before death on Jan 28, as follows

We recovered from the heart's blood gram-negative bacilli in pure culture. The autopsy findings were as follows:

Abdomen. There was a large quantity of yellow serous plastic exudate covering all organs. On the inferior border of the stomach were scattered hemorrhagic areas. The greater omentum was markedly injected. There was considerable injection of the mucosa of the pyloric portion of the stomach. The entire small intestine was markedly injected. There were scattered localized hemorrhages involving all surfaces of the intestines. Slight amount of serosanguineous fluid in pleural cavity. The lungs showed scattered, discrete, subpleural ecchymoses. There were a few scattered hemorrhagic areas in the right lower lobe.

Rabbit 5 was inoculated intraperitoneally on February 5, 1931, with ½ agar slant of the Bacillus 1C. The preliminary and subsequent counts were as follows

At 10 A.M. on Feb 7, 1931, a culture was taken from this rabbit's heart. Later a pure culture of a gram-negative, motile bacillus, similar morphologically to Bacillus 1C, was recovered. The rabbit was killed at 10.30 A.M. on Feb 7 and bone-marrow smears (figure 8) were made from the sternum. At the same time bone-marrow smears were taken from a normal rabbit (figure 7).

In the normal rabbit's bone-marrow there was a considerable preponderance of myeloid over erythroid cells, whereas, in in-

GUINEA PIG 19

DATE JAN 1931	WBC	NEUTROPHILS				SL	LL	MONO- CYTES	EOS. BASO	TEMP.
		(M)	(MM)	(S)	(SEG)					
27	10,000				5	95				100.4
28	1,000			5	10	85				94.6 (Dead)

GUINEA PIG 20

DATE FEB 1931	TIME OF DAY	WBC	NEUTROPHILS				SL	LL	MONO- CYTES	EOS. BASO
			(M)	(MM)	(S)	(SEG)				
	(Prelim)									
5	9 00 A.M.	11,400				26	61	4		9
6	4 30 P.M.	3,400				20	76	4		0
7	9 00 A.M.	3,100				25	73	2		0

jected rabbit 5 the predominating cells were erythroid. These characteristics are clearly shown in the following differential study of the bone-marrow of the normal rabbit and rabbit 5.

the convoluted tubules. In many of these there was complete chromatolysis, in others the nuclei were pyknotic and fragmented or pale and swollen. The glomeruli had escaped severe damage and the cells of the

BONE MARROW

	NORMAL RABBIT	RABBIT 5
1 Myeloid series		
Free histocytes	4	13
Eosinophil myelocytes	20	50
Heterophil myelocytes	147	98
Small lymphocytes	3	4
Heterophil leucocytes	2	3
Plasma cells	2	2
Reticular cells	1	0
Promyelocytes	11	22
Megacaryocytes	5	7
Monocytes	5	1
	<hr/> 200	<hr/> 200
2 Erythroid series		
Extruded normoblast nuclei	10	2
Hemocyto blasts	119	195
Hemocyto blasts in mitosis	2	3
Erythrocytes	195	225
Normoblasts	102	65
Syncytial reticular cells	6	3
Polychromatophil erythroblasts	44	6
Polychromatophil erythroblasts in mitosis	22	1
	<hr/> 500	<hr/> 500

In this connection it is to be remembered that the circulating blood of a normal rabbit contains 10 to 15 per cent eosinophilic leucocytes.

No marked gross changes were observed in rabbit 5 at autopsy. Microscopical examination. Liver. Intense congestion and marked parenchymatous degeneration evenly distributed, moderate amount of fatty degeneration, no cellular infiltration, the nuclei of the hepatic cells were slightly swollen and pale but were on the whole well preserved. Kidney. Very marked parenchymatous degeneration throughout renal parenchyma. The degenerative changes were most marked in

outer wall of Bowman's capsule and the emerging duct were approximately normal. No changes were seen in the endothelial cells. No cellular infiltration nor vascular changes were present. Spleen. There was swelling and edema of the reticular cells, no other abnormality. Lymph node. One small section of this showed changes similar to those in the spleen. Lungs. Negative except for congestion and edema. No hemorrhagic changes in any of the organs.

Guinea pig 20 was injected on March 18, 1931, intraperitoneally, with $\frac{1}{2}$ slant of gram-negative *Bacillus* 1B. A preliminary count was made on the morning before the

GUINEA PIG 20

DATE	TIME		WBC	NEUTROPHILS	CL	LI	EOSI	TRYP
MARCH	OF			(M MM S SFG)				
1931	DAY							
18	11 30 A M		11,600	32	62	4	2	101.6
18	4 00 P M		3,900	24	72	2	2	124

inoculation and another at 4 P.M. The guinea pig died that night

At autopsy 10 cc of serofibrinous fluid were found in the peritoneal cavity. The entire surfaces of both large and small intestines, which were covered with a thin purulent exudate, showed slight ecchymotic areas with occasional injection. The stomach was negative. The spleen and pancreas were negative. On the left lobe of the liver were five, small ecchymotic areas. The kidneys were negative. The heart was negative. The left lung showed generalized injection. The right lung was negative. The esophagus negative. A pure culture of gram-negative motile bacilli was recovered from the heart blood.

DISCUSSION

In this study of one case of agranulocytic angina, and the ensuing follow-up experiments, it was our hope to observe some factor which might be of interest and value in combating this

disease or in throwing light on its activities.

The rôle of the spleen in fetal and in post-natal hemopoiesis, its probable complementary correlation with the bone-marrow, its capability for myeloid metaplasia in myelosis and bone-marrow sclerosis,³ its almost uniform changes in leucopenic diseases, as well as the rarity with which septicemic diseases produce abscesses in its structures, led us to consider the likelihood of fetal spleen being of value in agranulocytosis. We feel as does Moynihan⁴ that the theory that spleen-pulp secretes a substance normally restraining white cell formation is entirely too superficial, and the experimental evidence to support it is not at all conclusive. Pfeiffer and Marx⁵ in investigating the formation of immune substances

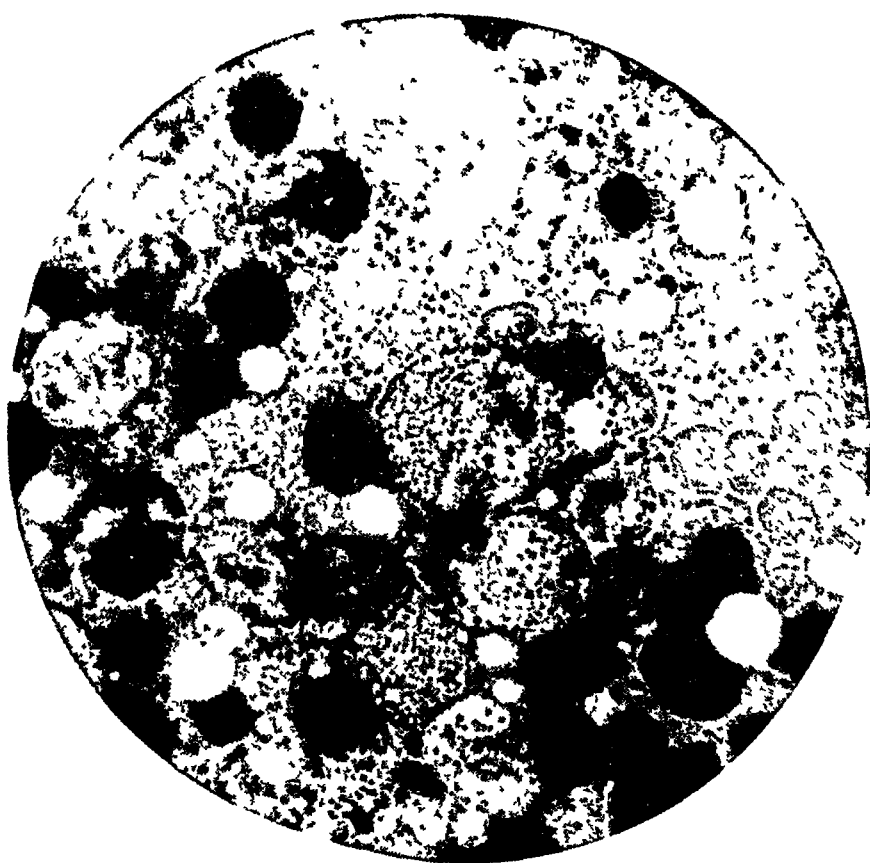


FIG 7 Bone-marrow of normal rabbit

in cholera found the spleen and the marrow of the long bones to contain a far larger proportion of immune substances than any other part of the body, and we know the resistance to infection is less in the early months after splenectomy. Also Hektoen⁶ affirms that antibodies are formed chiefly in the spleen, lymphatic tissues and bone-marrow. Carpenter⁷ in 1900 reported that splenic extract was of value in treating typhoid fever and malaria and found the leucocytes were increased.

In this case the use of fetal spleen was followed by an interesting reaction. Of course we do not know whether it was related or coincidental. In two

other cases of agranulocytosis to be reported elsewhere, there was an even more decisive and prompt rise in the polymorphonuclear leucocytes after the administration of fetal spleen. In one case of aplastic anemia, one case of severe leucopenia following deep roentgen-ray therapy, and two cases of myeloid leukemia, no changes were noted in the white cells, after giving fetal spleen over a considerable period.

Had the left external carotid artery been ligated earlier as a precautionary measure against hemorrhage from the left external maxillary artery, we feel that the patient might have recovered.

Specific agglutination tests (chart III) would indicate that the gram-

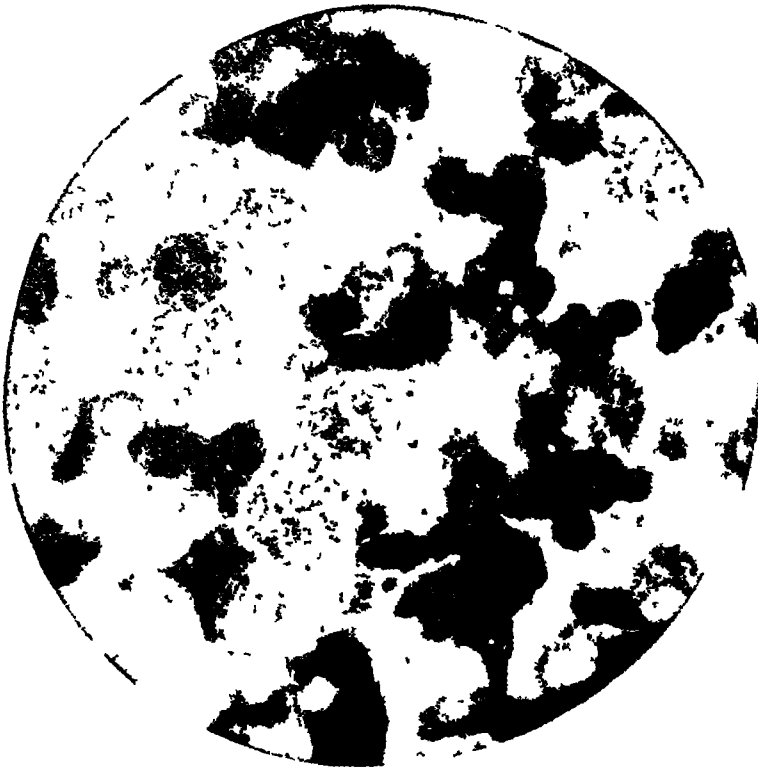


FIG 8 Bone-marrow of rabbit No 5, which developed a severe granulocytopenia following injection with *Bacillus* 1C. Note the striking depletion of myeloid cells.

Note that *Bacillus* 1A, *Bacillus* 1B, *Bacillus* 1C respectively were agglutinated by *Bacillus coli communior* serum, *Bacillus coli communior* was agglutinated by *Bacillus* 1C serum, which latter, also, agglutinated *Bacillus* 1A and *Bacillus* 1B.

CHART III
Agglutination Reactions

	IMMUNIZED SERUM				
	NORMAL RABBIT	B PYOCYANEUS	B 1C	B COLI COMMUNIS	B COLI COMMUNIOR
II Organism Tested					
1 Bacillus 1A	O	O	1-320 DIL. †	O	1-2560 DIL. †
2 Bacillus 1B	O	O	1-1280 DIL. †	O	1-640 DIL. †
3 Bacillus 1C	O	O	1-2560 DIL. †	O	1-640 DIL. †
4 B 2	O	O			
5 B 3	O	O			
6 B 4	O	O			
7 B Pyocyaneus	O	1-1280 DIL. †	O	O	O
8 B Coli Communis	O	O	O	1-640 DIL. †	O
9 B Coli Communior	O	O	1-640 DIL. †	1-320 DIL. †	O

LEGEND O Indicates no agglutination
 † indicates agglutination
 ‡ indicates fair agglutination

negative, motile Bacillus 1C should be classified as the *bacillus coli communior*. The gram-negative bacilli, 1A and 1B, obtained from the guinea pigs inoculated with the patient's blood, and from the necrotic tissue in the patient's mouth, respectively, possessed quite similar morphological, staining, cultural and fermentative reactions with the gram-negative bacilli 1C. We believe them to be the same organism. However, the bacilli 1B and 1C formed no gas with saccharose, whereas the pri-

mary bacilli 1A did. *Bacillus coli communis* forms no gas with saccharose but *bacillus coli communior* does. Bacillus 1B formed no gas with trehalose, which is at variance with its reaction with the colon group. All three organisms produced a small amount of gas with inosite, whereas the colon group ordinarily does not. These tests were repeatedly checked to insure their accuracy.

The cultural characteristics were similar to the colon group in the main details. However, the production of indol

by *Bacillus* 1A and *Bacillus* 1C was slight and with *Bacillus* 1B absent. There was also a slight, delayed liquefaction of gelatin. In these findings they differed from the colon group.

The gram-negative organisms, 1A, 1B and 1C, possessed definitely evident virulence and ability to repeatedly initiate a pronounced granulocytopenic blood reaction in guinea pigs and rabbits. In one rabbit, at least, very evident changes were noted in the myeloid elements of the bone-marrow at autopsy. It would seem in this case that the production of polymorphonuclear neutrophils in the bone-marrow was tremendously depressed.

The autopsy findings in eleven animals (ten guinea pigs and one rabbit) reflected certain findings in common. In the guinea pigs, which were injected intraperitoneally, the peritoneal cavity contained a moderate amount of serosanguineous fluid. The peritoneum was hyperemic, and a grayish-white, at times a yellowish, plastic exudation was noted. Especially on the peritoneal surface of the liver was the grayish-white exudate with hyperemic areas seen. In this locality the exudate was at times almost gelatinous in character, and ecchymotic spots were observed under the hepatic capsule. In the rabbit's liver parenchymatous degeneration and intense congestion were noted microscopically. There was also some fatty degeneration. There was no cellular infiltration. The small and large intestines were injected and hyperemic, and occasional areas of grayish-white exudate and ecchymotic spots were found. Especially about the ileum was this seen. Perforations were twice noted in the large

intestines. These perforations resulted from small perforating ulcers, arising from the mucous membrane, and were not traumatic. The mucous membrane, especially in the ileum, was hyperemic in three guinea pigs. In the rabbit's intestine no changes were noted macroscopically nor microscopically. On the gastric serosa, hyperemia, grayish-white exudation and rare ecchymotic spots were found. In one pig a small ulcer of the mucous membrane was found on the greater curvature near the pylorus. In one instance the gastric mucosa was injected with small hemorrhagic areas under the mucous membrane. The spleen in three animals (two guinea pigs and the rabbit) was somewhat swollen and very dark red in color. Swelling and edema of the littoral cells of the rabbit's spleen were quite apparent in the stained specimen. In this animal one lymph gland was sectioned and the same findings as in the spleen were noted. In five animals definite renal changes were observed consisting of swelling, subcapsular hyperemia, and blotchy localized hemorrhagic areas. In one pig a definite infarct was found in the kidney. In the rabbit's kidneys, parenchymatous degeneration, especially of the convoluted tubules, was found. No abnormalities were noted in the pancreas except in two cases, in one, some surface hyperemia, in the other marked injection and small hemorrhages throughout. In nine animals definite pathology was found in the lungs and pleurae. In six of these, serosanguineous, fibrinous exudation was noted in the pleura and in two, subpleural ecchymoses. Hemorrhagic areas moderately scattered throughout the lung tissue were noted

in five cases, in one guinea pig, a consolidated pneumonic area in the base of the right lung and in two, small hemorrhagic infarcts. Microscopically, considerable congestion and edema were noted in the rabbit's lungs and pleurae. No changes in the heart and thoracic vessels, esophagus, and trachea were observed. In every animal (ten guinea pigs and one rabbit) injected with the gram-negative *Bacillus* 1C, the organism was recovered from the heart's blood in pure culture following the animal's death. The bone-marrow of one rabbit showed a considerable depletion of myeloid cells, without any striking abnormalities of the erythroid cells. This was the only bone-marrow smear made.

There is considerable similarity between the necropsy findings in these animals and those of agranulocytic angina. In this latter disease the findings are: Subpleural and subpericardial hemorrhages, pleural exudation, hemorrhages and broncho-pneumonic areas in the lungs, cloudy swelling and fatty degeneration of the liver, moderate swelling and parenchymatous degeneration of the kidneys, some proliferation of the reticulo-endothelial cells of the lymph glands and spleen, depression of bone-marrow leucopoiesis, ulcerations of the gastro-intestinal tract, as well as in the oral cavity, vulva, vagina, cervix and rectum.

COMMENT

If we knew more about the pathogenesis of agranulocytic angina we might combat its ravages more successfully. We know that toxic substances expend their baneful power in several ways: some on the circulating leuco-

cytes, others upon their formative tissues; while a few act upon both. The action may be one of stimulation, so that a leucocytosis results, or it may be one of inhibition, and result in leucopenia. In pernicious anemia the poisonous action on the bone-marrow affects the white cells as well as the red cells, so that a very low white count is the rule, in hemolytic jaundice, on the other hand, the action on the bone-marrow is one of stimulation and leads to an out-pouring of leucocytes (leucocytosis). Florence Sabin³ has shown that leucocytosis involves both an increased delivery of cells from the bone-marrow (chemotactic factor) and an increased maturation of the delivered myelocytes (maturation factor) into the normal granulocytes (polynuclears, eosinophils and basophils). Therefore, this concept of leucocytosis and leucopenia postulates the infecting organism as introducing both a chemotactic and a maturation factor when a leucopenia follows a temporary leucocytosis. This condition has been proved to follow the injection of inactivated typhoid bacilli into a rabbit; the marrow and blood first show a leucocytosis, followed by a leucopenia. It has been proved that the mechanism of leucocytosis in an infection is due to an increase of the substances in the body that afford the normal stimulus, rather than some substance from the bacteria. The relationship of the degree of the leucocytosis to the resistance of an animal in infection has been repeatedly confirmed since Metchnikoff, and thus, as long as none of the substances involved in these reactions are known, variations in response of the body must be studied in terms of the amount of

the infection and, possibly, differences in the power of the hemopoietic tissues to respond. The reticulo-endothelial system is the locality for the formation of immune bodies, and as a part of that system the pulp-cells or the spleen are concerned in the manufacture of the immune substances with which the body resists infections. Immediately after splenectomy or in certain diseases with splenomegaly and leucopenia (kala-azar) it is impossible to develop immunity. It seems, therefore, that the spleen affords great aid in resisting infective processes. When we call to mind the frequency of pyemic and bacteremic states, the rarity of suppurative disturbances in the spleen is truly remarkable. It can only be explained on the assumption of strong bactericidal properties on the part of the spleen.

Pathological conditions in the bone-marrow may be divided into three groups: first, conditions of simple leucocytosis and leucopenia together with secondary anemia and aplasia, wherein no deviation is noted from the normal development of the cells; second, states like pernicious anemia and leukemia, in which immature cells come into the blood stream; third, conditions in which there has been an invasion of the marrow (replacement, necrosis, hemorrhage).

Normal bone-marrow architecture and normal bone structure have been found at autopsy in cases of agranulocytic angina. We observed in one of our cases the appearance of immature white cells (myelocytes, metamyelocytes) in the blood stream at the time of intense neutropenia. Although a greatly decreased number of granulocytes has been found in the bone-mar-

row at these autopsies we know that immature cells appear in the blood stream in more or less numbers. It would seem that there is an analogy between the state of the granulocytic function of the bone-marrow and the granulocytes in agranulocytic angina to that of the erythropoietic function of the bone-marrow and the red cells in pernicious anemia. However, since cases of agranulocytic angina recover and the blood stream returns to normal, the hypofunction must at times be temporary. Undoubtedly, either an infective or a toxic agent has temporarily paralyzed the granulopoiesis in the bone-marrow, or there is some substance which is lacking in the blood stream which would, if present, stimulate the bone-marrow to granulocytic activity. Of course, we know there is an intense infection present but the questions are, which is the primary organ involved, bone-marrow, spleen, reticulo-endothelial system, or, are several or all of them involved, or does the destruction of the mature granulocytes take place in the blood stream faster than the bone-marrow can manufacture them? If this latter condition were true we would find a considerable degree of granulocytic elements present in the bone-marrow in these cases. The reverse has been found, the marrow shows a striking depletion of granulocytic cells. We may assume therefore, that some other factor or factors are at work in the severe granulocytopenia than destruction of the leukocytes in the blood stream. We must look elsewhere. We have excluded the bone-marrow by the facts heretofore enumerated. Rosenthal and Spitzer² have shown that in the granulocytic an-

mal immune bodies develop normally, whereas, if the reticulo-endothelial system is blocked with colloid iron, immunity is greatly diminished, and, if the spleen is also extirpated, immunity ceases. The histopathology of the spleen in agranulocytic angina shows marked involvement of the splenic pulp (the reticulo-endothelial area). In most of the diseases characterized by a constant leucopenia there is a predilection for involvement of the splenic pulp. The Malpighian follicles show slight and inconstant changes in these diseases. If the spleen alone were involved in agranulocytic angina, the reticulo-endothelial tissues elsewhere in the body would soon take up its function of antibody formation, and this disease would, perhaps, not be so fatal. It would seem that the reticulo-endothelial system (in the spleen, liver, bone-marrow, lymph nodes, lymphoid tissue generally) is paralyzed by a toxic or infective agent, which may or may not be specific, and therefore immune bodies are not formed, and the granulocytogenic bone-marrow is not stimulated. In this connection it was interesting to note in the differential count of one of my cases, the increase of the monocytes (products of the reticulo-endothelial system) as the mature granulocytes (segmented forms) began to appear more abundantly in the blood stream as the patient improved, whereas they had previously disappeared. This of course shows evidences of re-

newed activity of the reticulo-endothelial tissues and increasing antibody formation. It was noted in this case that the monocytic cells began to increase in the blood stream six days before any increased signs of bone-marrow activity (increase in granulocytes) began. Antibody formation, it would seem, was beginning and the toxemia being combated. With the increasing control of the toxemia the severe effect of the infection on the bone-marrow granulopoiesis was lifted.

There is nothing impossible in conceiving that some toxins will affect the cells of the spleen-pulp, principally or exclusively, and cause degeneration therein. Then, the blood passing through the liver to the heart and lungs, without losing its toxic character, comes in contact with the cells in the sinusoids of the bone-marrow and may interfere with its granulopoiesis. If the toxin represses the bone-marrow granulopoiesis, leucopenia will result.

We would suggest that agranulocytic angina is not a disease entity, that it is a symptom-complex due to a paralysis of the reticulo-endothelial system from bacterial toxins, inhibiting or stopping the formation of some agent necessary for the stimulation of bone-marrow granulopoiesis.

It is with pleasure that I acknowledge the valued help of Dr Violet Keiller, Dr H N Gemoets, and our technicians, Mrs Louise M Blalock and Mr A W Owens, in this work.

REFERENCES

- ¹SCHULTZ, W. Berlin, Verein für innere Medizin und Kinderheilkunde, Deutsch med Wchnschr, 1922, xlviii, 1495.
- ²FRIEDMAN, U. Über Angina agranulocytica, Med Klin, 1923, xix, 1357-1359.

- ³DONHAUSER, J L. The human spleen as an haematoplastic organ, as exemplified in a case of splenomegaly with sclerosis of the bone-marrow, Jr Exper Med, 1908, x, 559-574.

- ⁴MOYNIHAN, SIR BERKLEY The spleen and some of its diseases, 1921, W B Saunders Company, Philadelphia
- ⁵PFEIFFER, R, and MARX Die Bildungs-
statte der Cholerascchutzstoffe, Ztschr f
Hyg, 1898, xxvii, 272-297
- ⁶HEKTOEN, L The influence of X-ray on
the production of antibodies, Jr Infect
Dis, 1915, xvii, 415-422
- ⁷CARPENTER, C R Splenic extract and the
splenic function, Med Rec, 1900, lvii,
273-277, The therapeutic action of splen-
ic extract in malarial infections, *ibid*,
1906, lxx, 165-169
- ⁸SABIN, F R Studies on blood, Johns Hop-
kins Hosp Bull., 1921, xxvii, 314,
Bone-marrow, *Physiol Rev*, 1928, viii,
191-244
- ⁹ROSENTHAL, F, und SPITZER, F Weitere
Untersuchungen über die trypanoziden
Substanzen des menschlichen Serums,
Die Bedeutung des Retikuloendothels
für den Mechanismus der trypanoziden
Wirkung des Menschenserums, Ztschr
f Immunitätsforsch u exper Therap,
1924, xl, 529-551

The Importance of Stressing Man as a Social Being

“ONE of the wholesome signs of our times is the increasing stress which we are placing on man as a social being. Yale University is founding an institute of human relations to study the individual in his contacts with people around him. A fundamental part of this study is the start which the infant and pre school child gets in adapting himself to those around him. Every healthy child begins life with an assertion of his ego. Unfortunately he often does not learn till manhood that he is not merely an individual, but a member of a group. Home, school, neighborhood, professional circle, social set make progressively greater demands on him to consider their rights and comfort and desires. Until he has learned this lesson he is not much good to anybody. The academic, business, and social worlds have little time or patience with human material that needs special processes to make it marketable.”

(From *Behavior Aspects of Child Conduct* by ESTHER LORING RICHARDS
The Macmillan Company, 1932. See also review in this issue.)

The Typhus-Spotted Fever Group

By NOXON TOOMEY, M D , F A C P., *Palmyra, Mo*

AMONG plagues of great economic importance, typhus fever has had a long and historically prominent place. Particularly during the Middle Ages, the Renaissance, and the early decades of the Industrial Era was typhus most prevalent. However, not even today is typhus a whit less devastating than formerly, whenever war, famine or civic commotion gives it an opportunity to override its barriers.

Typhus fever has, since 1837, been recognized as a disease entity, an exanthematic entity, without apparent kinship to the other exanthematic fevers, or the other continued fevers of short or long duration. Separated initially by Gerhard and Pennock, and by Still, independently, from other infections, by clinical means alone, the typhus did not become categorized with any of the older known diseases after bacteriologic methods afforded a means for establishing certain group relationships among the infections. This continuance of typhus as a unique type was due to the fact that there had not been, or at least not until very lately, any acceptable evidence concerning the identity of its pathogen. Thus typhus continued as a fever not only associated with famine and other civic calamities, but also as typically an acute exanthematic fever of unknown cause. It not infrequently

shared with cerebrospinal fever, and the Rocky Mountain spotted fever, the colloquial appellation of "spotted fever." It was natural, therefore, that the recently discovered fevers of spotted character and typhus-like course were studied in comparison with the typhus fever, and were more or less closely identified with the latter; the typhus always being advanced as the historically appropriate type of the group. The typhus-spotted fever group, although mentioned in a general way during the past few years, has not been discussed in a systematic or comprehensive manner. Hence there is need now to set forth, as well as possible, a summary of what may at present be recognized as the typhus-spotted fever group of diseases. However, as several of the fevers belonging to the group have been but imperfectly studied clinically, with data of bacteriological and immunological character completely wanting, it is not possible to do more at present than to call attention to the existence of the lesser known fevers, and to indicate in a general way their presumptive relationships as deduced from the meager data known concerning them. The purpose of this paper is, therefore, to present a concise survey or general portrayal of the group, with some special consideration given to the newly discovered (but by no means unimportant) diseases

that have not yet been accorded a place in general medical literature. As the better known diseases of the group have an easily available literature they will receive the briefest possible consideration consistent with this purpose.^{22, 40}

The typhus-spotted fever group may at present be set forth as comprising the following distinguishable entities and varieties

1 A—Typhus fever (louse borne and flea borne)

Old World (Classical) typhus (louse borne)

Baltic-Russian-Chinese strain

Balkan-Asia Minor strain

Tabardillo of Mexico and northwestern South America

Endemic Typhus (flea borne)

Brill's Disease of the eastern United States⁸

Endemic typhus of the southern United States (Maxcy)^{50, 56, 70}

Endemic typhus of western Europe (Netter and Blaisot)^{27, 52}

São Paulo strain (Piza and DaRocha-Lima)⁷⁵

Shop typhus of Malasia (Fletcher)^{84, 49, 95}

Endemic typhus of Australia (Hone)⁴¹

Endemic typhus of South Africa (Wicht)

B—Trench fever (louse borne)^{24, 11}

2 The Typhus-like tick fevers (tick borne)

Spotted fever of the Rocky Mountains

Malignant (Montana - Wyoming) type (Wilson and Chowning)

Intermediate (Gastrointestinal) type of Colorado and Utah (Becker)¹⁶⁴

Mild type (Maxcy)

Acute mild type (Idaho-Oregon)

Protracted mild type (Nevada-Utah)

Mid-zone strain (Kemp)²²³ (Toomey)²³⁰ (Reimann)²³¹

Typhus-like (Eastern - Southeastern States) type (Rumreich)^{217, 224}

Fièvre boutonneuse (exanthematic fever) (Conor and Bruch)

Kumaun tick typhus of the Himalayas (Megaw)

Tick-bite fever of Natal (Pretorian ten day fever) (McNaught)

Inuga fever of Portuguese East Africa (Kudicke)

Port Elizabeth fever of South Africa (Scroggie and Gray)

Guacarapa fever of Venezuela (García)

3 A—Tsutsugamushi disease (mite borne) Japanese-Korean flood fever (Palm)

Scrub typhus of Malasia (Dowden) (Noc)

Pseudo-typhus of Sumatra (Schuffner)¹⁰

Lymphatic pseudo-typhus (Mossman fever) of Queensland (Smithson)¹⁰

B—Ship (Rat mite?) typhus (Plazy, Marcon and Carboni) (Shelmire and Dove)^{11, 41}

C—a American mountain tick-fever (Toomey),²²⁵ b Benign rickettsial disease (Toomey)

4 Reduviid scarlatinosis (transmitted by Reduviidae)

Macular type (Toomey)

Acute lichen planus type²

HISTORICAL

It was by the students of the newly discovered typhus-like spotted fevers that comparative studies in this group were first undertaken. Thus the tabardillo of Mexico and the typhus-like fever described by Brill⁸ were studied in relation to Old World typhus, and were found to be of similar pathogenic (immunologic) nature, but to have fixed varietal differences (Anderson and Goldberger,^{9, 12} etc.) Similarly the spotted fever of the Rocky Mountains was soon after its discovery compared with tsutsugamushi disease, a spotted fever of Japan.³⁰ Likewise spotted fever of the Rocky Mountains was compared with typhus fever, with which it had been observed to have a somewhat general resemblance.^{9, 57, 64} It was not, however, until the tick borne typhus-like fevers became somewhat known (after 1917) and the flea borne strains of endemic typhus began to attract attention (after 1926) that there was a beginning laid for a typhus-spotted fever group.¹⁵⁰ The more recently widened knowledge of the mite borne group⁵⁴ of spotted fevers has so added to the group that it now seems possible to reconstruct the literature of the past twenty-five years into something like a systematic whole.

Although several of the diseases of the group have a clinical history extending back many years, it must be remembered that almost nothing was known concerning their mode of transmission, bacteriology, or immunology until very recent years, and that the conception of a spotted fever group did not begin to take scientific form until about seven years ago when the so-

called rickettsial group of diseases (typhus fever and Rocky Mountain spotted fever) began to be broached.¹⁵⁵ Since then, findings in the tsutsugamushi subgroup have definitely placed it among the fevers having rickettsial bodies as characteristic or almost characteristic elements in their histopathology.⁵⁰

For the purpose of forming a brief chronology, the chief discoveries that have served to establish the typhus-spotted fever group are given below. Only with regard to the more important discoveries can we take notice here.

GEOGRAPHIC DISTRIBUTION

Until a decade or two ago typhus fever was thought of only, or at least principally, in connection with the colder latitudes of the globe, it having been said not to exist in the tropics. This generalization is substantially correct for Old World typhus and for its variant, tabardillo of Mexico and the Andes. It is now known, however, that the governing consideration in the distribution of classical typhus is the climatic factor that conditions the survival of body lice,³ this factor being the absence of protracted, extreme heat. Against the flea borne endemic typhus, extreme heat is not a barrier, hence endemic typhus can occur wherever the flea (particularly the rat flea) is found. As fleas have an almost world wide distribution, being actually more common in the warmer temperate and torrid zones, endemic typhus is potentially almost cosmopolitan, with slight varietal differences being recognizable according to locality. These slight differences of strain are, however, almost entirely of serologic character, clinical

TABLE I

Chronology of Discoveries in the Typhus-Spotted Fever Group

TYPHUS FEVER SUBGROUP (LOUSE BORNE AND FLEA BORNE)	SPOTTED FEVER SUBGROUP (TICK BORNE)	TSUTSUGAMUSHI SUBGROUP (MITE BORNE)
1908 Yersin and Vassal transmitted typhus from man to man by blood inoculation, and expressed opinion typhus was transmitted by insect bites	1902 Wilson and Chowning report on malignant type of Rocky Mountain spotted fever, and suspect ticks as vectors	1907 Tanaka showed that the blood of a man ill with tsutsugamushi disease is infectious
1909 Typhus transmitted from man to man by body lice (Nicolle, Compte and Conseil)	1906 Ricketts demonstrates presence in nature of ticks infected with spotted fever, and hereditary passage of virus through eggs	1908 Yersin described clinically a typhus-like disease from Cochin China
1910 Endemic typhus of eastern U S described by Brill as distinct disease	1908 Tick transmission of Rocky Mountain spotted fever to man reported by McCalla and Brereton	1910 Lymphatic pseudo-typhus (Mossman fever) described clinically by Smithson
1910 Tabardillo and Rocky Mountain spotted fever shown to be different diseases (Ricketts and Wilder)	1909 From Rocky Mountain spotted fever material Ricketts describes intracellular organisms later known as rickettsia bodies in his honor	1912 Tidswell reports on Mossman fever
1910 Tabardillo virus shown to be nonfilterable by Ricketts and Wilder, described as bodies like ones found by Ricketts in spotted fever	1910 (See under typhus)	1913 Mossman fever studied by Clark
1912 Anderson and Goldberger identify Brill's disease and tabardillo as being varieties of same disease	1910 Fievre boutonneuse described from Tunis by Conor and Bruch	1914 Breinl, Priestley and Fielding report on Mossman fever
1914 Sergeant, Foley and Vialette describe rickettsia found only in lice collected from typhus cases	1911 Pathologic anatomy of Rocky Mountain fever described by LeCount	1914 Pseudo-typhus of Deli Sumatra described clinically by Schuffner, ticks being suspected as vectors
1915 Trench fever described by Graham	1911 Tick-bite fever of Africa described clinically by McNaught	1915 Dowden gives brief clinical description of scrub typhus of Malasia
1916 Immune serum against typhus, fairly effective for laboratory animals, developed by Nicolle and Blaisot	1916 Wolbach describes <i>Deimacentronus rickettsi</i> a rickettsial organism, as pathogen of Rocky Mountain spotted fever	1917 Tsutsugamushi disease transmitted to man by larval mites (Miyajima)
1916 DeRocha-Lima describes <i>R. prowazeki</i> as found in typhus transmitting lice, but never in typhus free lice and considers it pathogen of typhus fever	1917 Tick typhus described clinically from northern India by Megaw	
1916 Toepfer finds rickettsia in trench fever lice and associated them etiologically with the fever		
1917 Weil and Felix introduce the <i>Proteus X₁₉</i> agglutination test for typhus fever		

TABLE I (Continued)

TYPHUS FEVER SUBGROUP (LOUSE BORNE AND FLEA BORNE)	SPOTTED FEVER SUBGROUP (TICK BORNE)	TSUTSUGAMUSHI SUBGROUP (TICK BORNE)
1917 Neill describes scrotal lesion of tabardillo in guinea pigs	1920 Carducci and Falcone independently describe <i>fièvre boutonneuse</i> in Italy as special form of eruptive fever	1920 J A Mitchell describes mild typhus-like disease in Transkei, South Africa
1918 Brill's strain of endemic typhus recognized in western Europe by Netter and Blaizot	1921 Inuga fever described from Portuguese East Africa by Kudicke, ticks being incriminated on clinical evidence	1923 Prates in Lourenço Marques describes typhus-like disease with primary ulcers
1918 Proteus X-strains demonstrated not to be pathogen of typhus fever nor to immunized laboratory animals against the disease	1923 Rocky Mountain spotted fever organism grown in tissue culture (see under typhus subgroup)	1923 Cowdry reports on distribution of rickettsiae in tissues of insects and arachnids
1919 Pathology of typhus described by Grzywo-Dabrowsky (1918) and by Ceelen	1923 Noguchi finds three strains of rickettsiae from spotted fever ticks to be non-pathogenic	1924 Spencer and Parker recognize phases of latency and activity of spotted fever virus in ticks, and report on virus in blood
1919 Bradford, Bashford and Wilson claim to have cultivated the rickettsial organisms of typhus and of trench fever	1925 Balfour, Clearkin, Anderson and Clark redescribe typhus-like fever of South Africa, and incriminate ticks as vectors	1926 Nagayo describes a rickettsia as cause of tsutsugamushi disease
1919 Two commissions — English War Office, and American Commission study trench fever	1925 Guacarapa spotted fever of Venezuela described clinically by Garcia	1927 Frill at Potchestroom, South Africa, describes a typhus-like disease
1919 Typhus caused by <i>R prowazeki</i> , and trench fever by <i>R quintana</i> , according to Arkwright, Bacot and Duncan	1927 <i>Fièvre boutonneuse</i> recognized on French littoral by Olmer, and by Boinet and Pieri, insect transmission being suspected	1928 Tsutsugamushi virus cultivated in testicle of living rabbit by Ogata and by Ishiwara
1922 Endemic typhus in Australia described by Hone	1927 Spencer and Parker develop a spotted fever vaccine prophylactically effective for man	1930 Scrub typhus of Malasia studied immunologically and clinically by Fletcher
1923 Wolbach and Schlesinger report cultivation of organisms of typhus and of spotted fever in tissue and plasma cultures	1928 Cooley reports on tick parasites	1930 Marcandier and Bidreau study ship typhus and incriminate a rat acarus as the possible vector
1926 Kuczynski and co-workers publish biological and pathogenetic studies on rickettsiae in typhus and Rocky Mountain spotted fever	1930 African tick-bite fever transmitted to guinea pigs by Pijper and Dau	
1926 Endemic typhus in southern portion of U S described by Maxcy, who incriminates fleas as vectors		
1930 Mooser and Dummer find rickettsia in tunica vaginalis of guinea pigs infected with endemic typhus		

TABLE I (Continued)

TYPHUS FEVER SUBGROUP (LOUSE BORNE AND FLEA BORNE)	SPOTTED FEVER SUBGROUP (TICK BORNE)	TSUTSUGAMUSHI SUBGROUP (MITE BORNE)
1931 São Paulo strain of endemic typhus described by Piza, DaRocha-Lima and associates	1930 Rickettsia described in skin lesions of fièvre boutonneuse by Durand, Kuczynski and Hohenadel	1930 Lewthraite reports on epidemiology of scrub typhus of Malasia
1931 Mooser, Casteneda and Zinsser demonstrate endemic typhus reservoir in wild rats	1931 Rocky Mountain spotted fever found to be in southeastern U S endemic area by Badger, Dyer and Rumreich	1931 Wolff reports on immunology of pseudo-typhus of Sumatra
1931 Pinkerton and Maxcy describe anatomical pathology of endemic typhus in man, with <i>R. prowazeki</i> in vascular lesions of human brain	1931 American Mountain tick-fever recognized as entity distinct from Rocky Mountain spotted fever by Toomey	1931 Marcandier and associates demonstrate absence of cross immunity between ship typhus and fièvre boutonneuse
1931 Nagayo cultivates typhus organism in living rabbit eyes (see under tsutsugamushi disease)	1931 Fièvre boutonneuse immunologically distinguished from ship typhus by Marcandier, etc	1931 Nagayo and associates describe rickettsiae from typhus and tsutsugamushi in tissue cultures, with use of eyes of living rabbits as culture medium
	1932 Virus of fièvre boutonneuse stated to be filterable by Blanc and Caminopetros	1931 Dove and Shelmire draw attention to tropical rat mites as possible vectors of endemic typhus

differences being wanting, trifling or inconstant

As to the tick borne typhus-like fevers there is a somewhat more striking geographic correlation than with the louse or flea borne diseases. Within the tick borne subgroup we are brought to recognize the more limited distribution of ticks, not perhaps as a class, but as to the actual species that are vectors of the tick borne typhus-like spotted fever, or fevers. Here we observe the highly localized character of certain tick borne fevers, the localization often being correlatable with certain definite mountain slopes and the adjacent wooded waste lands. Two, at least, of the tick borne typhus-like fevers, spotted fever of the Rocky Mountains and fièvre boutonneuse of the Mediterranean, have in recent years apparently spread over an area wider than their original habitat. Of the other fevers of this subgroup not

enough is known to be able to state to what extent their distribution is limited, or will be kept in check by conditioning factors peculiar to their present habitat.

Concerning the mite borne diseases we have to note the very interesting fact that they are positively known up to the present time only in that portion of the world embracing eastern Asia, Malasia and the adjacent portion of Australia. A possible exception is ship typhus which has been suspected, but not proved, to be transmitted by the tropical rat mite, *Liponyssus bacoti*, Hirst^{67, 68}. A possible case of tsutsugamushi disease occurring in the mandated territory of New Guinea was described by Sinclair in 1930.⁶⁹

CLINIQUE AND COMPARATIVE SYMPTOMATOLOGY

The nosography of the typhus-spotted fever group, up to very recently

has rested almost solely on a clinical basis for want of sufficient data concerning the bacteriology, immunology and anatomical pathology of the various members of the group. Serologic-immunologic studies have, however, within the past five years, and particularly within the past two years, contributed to a more exact knowledge of the relationships of these diseases. The three most significant results of these immune serum studies have been to show that (1) Those diseases clinically recognizable as dissimilar, are actually so from the standpoint of being different pathogenic entities, (2) that so far, at least, the prime division of the group according to the biologic order of the insect vectors concerned is a valid mode of classification, and (3) that for each disease one or more varietal strains can be made out serologically, without an always correlatable disparity in clinical course, appearance or duration.

The comparative symptomatology of the diseases that comprise the typhus-spotted fever group can best be interpreted by considering the lymph-blood-vascular (particularly the lymph system) and the cutaneous reactions to these diseases. Prostration (often severe, and with coma), rheumatoid pains (often severe), and a tendency to muscular spasticity are almost constant phenomena in varying degrees, but they do not afford as objectively differentiating evidence for classification as do the lymph-blood-vascular and cutaneous reactions. In fact it may be said that as far as is now known, the anatomical pathology of the typhus-spotted fever group is primarily and almost exclusively limited to the circu-

latory system, particularly the lymphatics and the smaller and smallest blood vessels. Dry bronchial inflammation and cerebral toxic manifestations occur in the most severe fevers of this group, but they are rather consequential than primary lesions.

The comparative symptomatology of the diseases of the typhus-spotted fever group can be correlated in a general way with the vectors implicated, thus a primary lesion at point of inoculation is not observable in the louse borne and flea borne diseases, is observable in some but not all of the tick borne diseases, and is virtually a constant phenomenon in the mite borne diseases. Secondary regional lymphangitis and lymphadenopathy is not a part of the louse and flea borne diseases, is absent, inconstant, or not well developed in the tick borne diseases, but is distinctly a characteristic of the mite borne group of fevers. While the latter show both a primary lesion and a regional lymphangitis-lymphadenopathy, it should be noted that the two are not constant accompaniments of one another, the tsutsugamushi disease and scrub typhus of Malasia having a practically constant primary patch but a less determined lymphadenitis, whereas the pseudo-typhus of Sumatra and lymphatic pseudo-typhus (Mossman fever) of Queensland have a constant and well marked disposition to lymphadenopathy, but with a less well accentuated primary sore than in tsutsugamushi disease and scrub typhus of Malasia.

In regard to the cutaneous lesions of this group one must remark a strong family resemblance, particularly within each subgroup. Thus the manner of appearance and distribution of rash can

not be invoked as a clearcut, dependable basis for differentiation. Despite individual variations and a strong family resemblance, there can, however, be made out certain broad distinctions even between diseases of the same subgroup. Thus, in the louse and flea borne subgroup one remarks the rash of tabardillo to be usually less papular, larger and distributed more on the lower part of the body than in classical typhus. Endemic typhus, which on the whole is milder than classical typhus (although exceptions occur), has as a rule a somewhat smaller lenticular lesion with a lesser tendency to become petechial, it may be, but usually is not, quite as profuse as in classical typhus, and is not as commonly accompanied by a diffuse scarlatinoid (reticular) blush. Within the tick borne group one finds in Rocky Mountain spotted fever that the rash (accompanied by a diffuse cyanotic blush in severe cases) shows marked passive congestion, and appears on the wrists and ankles, spreading upwards as edematous but compressible macules that usually spare the face. In *fièvre boutonneuse* the rash is much more papular (infiltrated) than in spotted fever, appears first on the face or upper part of the trunk, is larger, more sparsely set, and of longer duration considering the comparative intensity and duration of the two fevers. Kumaun tick typhus has characteristics of both Rocky Mountain spotted fever and *fièvre boutonneuse*, but more closely resembles the latter. Tick-bite fever of South Africa resembles somewhat the *fièvre boutonneuse* but also has some of the features of the mite borne diseases. Within the mite borne subgroup the rash is approximately the

same in all the clinical types, but tends to be less pronounced in scrub typhus and pseudo-typhus of Sumatra than in Japanese flood fever. In lymphatic pseudo-typhus the rash has a vesicular tendency.

Respecting the incubation period, mode of onset, duration, severity of muscular pains and intensity of prostration there are equally as wide or wider variations than among the circulatory and cutaneous lesions. Thus we find a shorter incubation period in the louse and flea borne subgroup than in some of the tick borne diseases, and a still longer incubation period in one (or sometimes two) of the mite borne diseases. The mode of onset and severity of muscular pains are roughly correlatable with the ultimate severity of the disease, but even here we find that tsutsugamushi disease develops intense prostration at a somewhat slower rate than the malignant forms of the louse borne and tick borne fevers.

Toxemic symptoms as manifested by cerebral disturbances and circulatory collapse may occur in any of the severer fevers of the typhus-spotted fever group, but they are rare in some, average in others and well nigh constantly fatal in others. Thus the mortality rate differs greatly within the group, but rather according to the type of the disease under consideration than for the disease as a whole, a matter particularly well exemplified by spotted fever of the Rocky Mountains, certain epidemics of typhus fever, and occasionally by Japanese-Korean flood fever. Nor can it be said that there is great disparity in the mortality among the three great subgroups, each

having grave as well as mild diseases, but of the three the mite borne are collectively both somewhat less fatal and less of a world problem than the tick borne, flea borne, or louse borne diseases

The comparative semeiology of the several diseases, and their more distinctive varieties, are briefly summa-

rized in the accompanying table (see table II) For a fuller description of the tick borne diseases see a subsequent article entitled "The Tick Borne Typhus-like Fevers".

BACTERIOLOGY

In common with practically all diseases of a zymotic character, typhus

TABLE II

LOUSE AND FLEA BORNE	SEASONAL	INCUBATION PERIOD	MODE OF ONSET	PRIMARY SORE	RASH
OLD WORLD TYPHUS	Winter chiefly, or any time	10 to 14 days Mostly 12	Abrupt with rigors, headache, myositis	No	3d to 5th day, Subcuticular, and petechial papules
ENDEMIC TYPHUS	Spring to early Fall	10 to 14 days	Subabrupt or abrupt, like mild typhus	No	Frequently but not commonly petechial
TRENCH FEVER	Any time, winter chiefly	6 to 8 days, may be 30 days after exposure	Sudden with giddiness, dyspnea	No	Delicate small, red macules on chest, abdomen
TICK BORNE					
ROCKY MOUNTAIN SPOTTED FEVER MALIGNANT TYPE	Early spring to mid-summer	5 to 10 days mostly 7	Abrupt with dull headache, conjunctivitis, vomiting and severe rheumatoid pains	No	Appears 3d or 4th day as red macules on ankles and wrists, spreads upwards becoming cyanotic-petechial
MILD TYPE	Early spring to mid-summer	7 to 10 days	Fairly abrupt rheumatoid pains, etc	No	3rd to 5th day spreads upwards, cyanotic-petechial
BENIGN RICKETTSIAL DISEASE*	Late spring and summer	10 to 14 days mostly 12	Sudden with headache, chilliness, nausea	No	Very rare, somewhat like mild R M S F
AMERICAN MOUNTAIN TICK-FEVER	Early spring to September	3 to 7 days mostly 4	Sudden with headache, chilliness, bone pains, nausea	Often Yes	No
FIEVRE BOUTONNEUSE	Only in late spring and summer	5 to 15 days mostly 8	Fairly abrupt rheumatoid pains	Yes but not always	Large hard papules on 3rd day, on face thence downward, palmar and plantar lesions, hemorrhagic tendency slight

(also tsutsugamushi disease) was early the subject of numerous bacteriological investigations made according to the methods available during the first decades of bacteriology. Numerous were the organisms found in, and at times identified etiologically with typhus material. For our purpose, however, it would serve no useful end to review

the early reports on the bacteriology of these diseases, as now the reports have only historical interest. While some of the early workers may have observed organisms of rickettsial character, they failed to bring forth proof of an etiologic relationship of these minute bodies to the diseases in which they were encountered. Even in spotted

TABLE II (Continued)

COMA	DURATION OF FEVER	MODE OF TERMINATION	CON-VALESCENCE	IMMUNITY	MORTALITY
Very frequent, early	10 to 18 days mostly 14 days	Crisis or abrupt lysis	Usually rapid, occasionally with relapses	Absolute	12 to 40 per cent, Average 19%
Frequent, often transitory	12 to 15 days	Abrupt lysis	Rapid and without relapses	Relatively absolute	5 to 12 per cent
No	35 to 42 days occasionally 5 to 9 days, relapsing	Gradual lysis	Moderately rapid	No	0
Almost invariable early, profound	Usually fatal 5th to 9th day (average 7th day) Survivals run 21 to 26 days	Subabrupt lysis	Slow, occasional relapses, gangrenous sequelae	Absolute	85%
Mild, very occasional	21 to 28 days	Lysis	Fairly rapid, frequently slow	Considerable but for mild type only	4 to 20% Average 15%
No	5 or 6 days followed by one-day remission	Rapid lysis	Rapid	?	0 ?
Light stupor and delirium	2 or 3 days followed by one or more irregular remissions	Lysis, usually rapid	Usually fairly rapid	?	About 0.5%
No	12 to 17 days mostly 14 days	Lysis	Moderate in young, gradual in elderly	Moderate transitory	Under 1%

TABLE II (Continued)

LOUSE AND FLICA BORNE	SEASONAL	INCUBATION PERIOD	MODE OF ONSET	PRIMARY SORE	RASH
KUMAUN TICK TYPHUS	Late spring and early summer	14 to 21 days	Gradual	Yes	Profuse, ap- pears 5th day on upper trunk, pe- techial by 8th day
INUGA FEVER	?	?	Sudden with chills, head- ache, con- junctivitis	Yes	Pea sized, red- dish morbilliform macules Begins 1st day, developed by 5th
GUACARAPA FEVER	?	?	Similar to Rocky Moun- tain spotted fever	No ?	Closely resembles Rocky Mountain spotted fever
TICK-BITE FEVER OF NATAL	Probably in only spring and summer	8 to 10 ? days	Sudden with severe head- ache	Yes	Profuse dark red morbilliform, on 3rd to 6th day
RHODESIAN FEVER*	Summer and autumn	?	Suddenly with shivering and headache	Yes	4th or 5th day universal maculo-papular non-petechial
PORT ELIZA- BETH FEVER*	February to July	?	Sudden or subabrupt; headache	No	In 50% only, sparse macules
MITE BORNE					
JAPANESE FLOOD FEVER	Middle of July to October	4 to 10 days	Rapid with rigors, front- al headache	Yes	5th to 7th day as papules, spreads downwards chiefly as macules on body
SCRUB TYPHUS OF MALASIA	No	11 to 21 days	Abrupt shivering headache	No	4th to 6th day, maculopapular on chest, ab- domen
PSEUDO- TYPHUS OF SUMATRA	June to Aug Nov to Jan	12 to 16 days	Rapid	Yes	Roseolar, univer- sal, but mostly on trunk and flanks Fades slowly, sometimes hemor- rhagic
LYMPHATIC PSEUDO- TYPHUS	?	6 to 10 days	Sudden or gradual	Yes but not always	Macular or ves- icular
SHIP TYPHUS	Any time mostly summer	About 10 days	Sudden but usually mild	No	Resembles mild endemic typhus
EX-REDU- VIIDAE					
REDUVID SCARLA- TINOSIS	Summer June and July	5 to 7 days	Fairly abrupt initial symp- toms mild	Yes not well marked	Macular exuda- tive, scarlatinoid face-limbs chiefly

*Vector uncertain

TABLE II (Continued)

COMA	DURATION OF FEVER	MODE OF TERMINATION	CON-VALESCENCE	IMMUNITY	MORTALITY
?	10 to 14 days mostly 12 days Paratyphoid type	Lysis	Rapid	?	5 to 10 per cent
Exceptional	7 to 10 days	Crisis or rapid lysis	Rapid	?	0 ?
?	Usually fatal 7th to 9th day	Crisis or lysis	Rapid	?	High
?	8 to 11 days	Rapid lysis	?	?	0 ?
Light stupor, delirium	10 to 14 days 2d rise after eruption	More or less rapid lysis	Usually rapid without sequelae	?	About 7%
No	8 to 14 days, low, irregular, occasionally high	Rapid lysis	Rapid	?	0 ?
Frequently, late	20 days	Lysis	Usually quick	Very considerable, somewhat transitory	30%
Yes, or delirium in even mildest cases	fever may be low, 14 days	Lysis	Moderate broncho-pneumonia common sequel	Lasting	4 to 14 75% Average 6 75%
Frequent, or delirium	11 to 15 days, typhoidal with nervous symptoms	Lysis	Fairly rapid Pulmonary complications	Yes	6 to 8%
No ?	3 to 21 days	Lysis	?	Slight	Under 1%
Very exceptional	8 to 12 days	Rapid lysis	Rapid	Moderate	1 to 2%
May occur	7 to 21 days mostly 10	Rapid lysis	Slow	?	Probably 3 to 5%

fever Anderson probably anticipated Ricketts in observing the minute microgametic life that is causal of spotted fever, but he did not carry his observations to a practical conclusion.

Howard Taylor Ricketts in 1909 described minute intracellular organisms in spotted fever material, referring to them as bodies that could be associated not only with spotted fever but also with the known vector of the disease, the tick *Dermacentor andersoni*, and transmitted through the eggs of the latter from one generation to another.⁶² A year later, working with typhus fever material in Mexico, Ricketts observed in typhus infected lice and in typhus material, intracellular organisms of a character similar to the bodies he had described in connection with spotted fever of the Rocky Mountains.⁶ Unfortunately his untimely death from typhus fever closed for him one of his major investigations. However his work was taken up by Hegler and von Prowazek¹⁸ in connection with typhus, and by S. Burt Wolbach in connection with spotted fever of the Rocky Mountains.¹⁰⁷ Von Prowazek, likewise dying of typhus fever, did not live to complete his studies, it becoming the good fortune of Sergeant, Foley and Vialette, in 1914, to describe rickettsia peculiar solely to lice known to be venemous with typhus fever.¹⁸ They, however, cautiously refrained from claiming a proven etiogenic relationship for these organisms. Two years later DeRocha-Lima confirmed these observations and claimed an etiologic rôle for the organism, which he named *Rickettsia prowazeki*.¹⁵ Subsequent studies made with a louse, *Pediculus longiceps*, and *Macacus rhe-*

sus monkeys enabled Arkwright, Bacot and Duncan, in 1919, to state that the etiologic rôle of *R. prowazeki* for typhus was so circumstantial as to be all but proven, as the lice they were working with, normally not carriers of rickettsia, became infected with *R. prowazeki* when allowed to feed on monkeys suffering with typhus fever.⁷² Weigl in the meantime having introduced the ingenious method of feeding lice by anus,¹⁴ Atkin and Bacot, in 1922, proved that *R. prowazeki* developed in *Pediculus longiceps* after feeding on typhus infected monkeys and after rectal injections of blood from typhus cases, thereafter being able to cause typhus fever in monkeys.⁴¹ The method of Weigl, employed by Atkins and Bacot, was equivalent to the living culture medium method defended by Wolbach in 1925.¹⁵⁶ Since the equivalent fulfillment of Koch's postulates by Atkins and Bacot, numerous studies have been carried out on *R. prowazeki*, the chief ones being by Weigl, Wolbach and Schlesinger, Kuczynski and his coworkers,⁴³ and more recently those by Nagayo in the eye of the living guinea pig,⁷¹ and by Nigg and Landsteiner in tissue culture.⁸³

Whether or not the organism recovered from active typhus fever cases by Plotz, Olitzky and Baehr,^{14,23} is an anaerobically cultivatable form of *R. prowazeki* has never been definitely established, but the present weight of evidence is against such a supposition.⁸⁰

Weil, in 1915, noted a fairly constant non-saprophytic occurrence of yet another organism, a *Proteus* bacillus (two strains, X₁ and X₂) in con-

nection with active typhus fever cases. Although these strains of *Proteus* were agglutinated by high dilutions of sera from cases of typhus fever during the fastigium, it was early proved that neither strain was capable of producing typhus fever in non-immune laboratory animals or in man. Also it was shown by Landsteiner and Hausmann,²⁹ by Dorr and Pick,³⁰ and by Möllers and Wolff,³¹ to be incapable of immunizing susceptible laboratory animals against typhus fever. Thus the rôle of the *Proteus X* strains to typhus fever was early recognized as being of unknown character despite the fact that Dienes²⁸ recovered these organisms from the blood of typhus fever patients in 30 per cent of the cases which he examined. This relationship of *Proteus X* strains to typhus fever has not been clarified to date although Schultz³² and others have expressed the opinion that the body louse can and probably does more or less frequently inoculate man with other organisms simultaneously with the rickettsial infection.

This brief résumé of the virus studies on typhus fever will be closed by noting that a negative phase of the problem has been set forth by Brumpt, by Weigl, by Noguchi and others, who have shown that non-pathogenic rickettsias also occur in lice as in other arthropods. These non-(typhus) pathogenic rickettsias of lice are for the present grouped under the name of *R. pediculi*, and are believed to be identical with *R. quintana* and *R. wolhynica*, the trench fever rickettsias of the body louse. In regard to the other extracellular rickettsias from mallophaga, etc., Wolbach states that there is very

little if any reason for regarding them as different from familiar bacteria. These organisms have been cultivated on blood agar media by Noller in 1917,¹⁷ and by Sikora in 1921.³⁴

Spotted fever of the Rocky Mountains was the second typhus-like disease to be more conclusively associated with rickettsia. This was accomplished by Wolbach,¹⁰⁷ and by Wolbach and Schlesinger,¹²⁷ by pathological studies, by comparative tick studies, and by proving tissue-plasma cultures of the organism to be virulent for spotted fever.¹¹³ The organism has also been cultivated (?) by Kuczynski and by Otto and has been found in spotted fever rabbit material by Connor,¹⁴⁰ by Nicholson,¹²⁶ and by Reimann.¹⁵¹ Subsequent work on the virus has been by Spencer¹³⁸ and Parker,¹⁵⁸ who have however, confined themselves to the immunological aspects of the virus.

Trench fever was the third rickettsial disease to be placed on a reasonably acceptable bacteriological basis.²⁴ This was accomplished by Bacot³⁷ in 1921 despite the previous report of the American Trench Fever Commission which held to a filterable virus as the cause of trench fever.²⁵ Bacot's observations, however, await confirmation.

Nagayo in 1926 was the first to state that tsutsugamushi disease was caused by an organism referable to the rickettsial group. Subsequent tissue culture studies by Ishiwara and Ogata,¹¹ employing the living rabbit testicle, and by Nagayo⁵⁹ employing the living rabbit eye have established the etiologic relationship of the organism which has been named *R. orientalis*. Nagayo, 1926.

As to *fièvre boutonneuse* (exanthematic fever) P. Durand, Kuczynski, and Hohenadel stated in 1930 that they observed rickettsia bodies in the cutaneous macules of the disease in man. Georges Blanc and J. Caminopetros reported, however, in 1932, that the virus of *fièvre boutonneuse* is filterable through the Chamberland candle L.

The other diseases of the typhus-spotted fever group, namely Kumaun Tick Typhus, Tick-bite Fever of Natal, Inuga Fever, Guacarapa Fever, Scrub Typhus of Malasia, Pseudo-typhus of Sumatra, Lymphatic Pseudo-typhus of Queensland, Port Elizabeth Fever, Ross's Rhodesian Fever, Ship Typhus, and Reduviid Scarletosis, have an unknown bacteriologic status.

The rickettsial origin of endemic typhus has been recently more conclusively demonstrated by Mooser and Dummer, who, in 1930, found rickettsia in the tunica vaginalis of guinea pigs infected with endemic typhus,⁶⁸ and by Pinkerton and Maxcy who found *R. prowazeki* in vascular lesions in the brain of a man dead of endemic typhus (or spotted fever, eastern type).⁸²

IMMUNOLOGY

Apart from considerations resting upon the morphologic and cultural characteristics of the minute intracellular organisms so definitely associated with the rickettsial group of diseases, there has been woven an extremely interesting and important web of evidence consisting of the serologic reactions constantly proper, and more or less differentiating, to each of the diseases (or at least subgroups) of the typhus-spotted fever group. In fact

it is immunological rather than bacteriological evidence that confirms clinical evidence in the case of several of the tick borne typhus-like fevers.

The immunologic studies that have been made in this group, for diagnostic purposes, may be divided into animal inoculations (cross immunity tests) and bacterial agglutination reactions. The immunologic studies for prophylactic^{16,47,63} and therapeutic purposes^{16,21} have so far had to do only with typhus fever, and spotted fever of the Rocky Mountains. A potent therapeutic serum or vaccine, available for man, has not yet been developed for any disease of this group. Prophylactically, however, the chemically attenuated virus vaccine for spotted fever of the Rocky Mountains, as developed by Spencer and Parker, is of great value, and has recently been discussed at length by the author.²⁸³

The cross immunity tests, utilizing guinea pigs chiefly, has been applied to distinguishing Rocky Mountain spotted fever from classical typhus fever,⁶⁴ endemic typhus, and tsutsugamushi disease, and in distinguishing classical typhus and endemic typhus from *fièvre boutonneuse*.

The agglutination tests depend upon furtherance of the observations of Weil and Felix²⁵ that typhus serum agglutinates in high dilution a strain of proteus bacillus denominated *Proteus X₁₀* (a variant of which is also referred to as the Warsaw strain). Thus, the Weil-Felix test, has been extensively applied to all, or almost all of the diseases of the typhus-spotted fever group. It has been found strongly positive in some of the diseases (classical typhus, tabardillo, Brill's

disease, ship typhus of Malasia, and ship typhus of Toulon), moderately positive in others (Rocky Mountain spotted fever, fièvre boutonneuse, "typhus" in Kenya, and occasionally but rarely in Kumaun tick-typhus of India), and absent in still others (tsutsugamushi disease, scrub typhus of Malasia,^{61,63,65,66} and pseudo-typhus of Sumatra^{73,74}) it is observable that agglutination occurs against a non-indologenic strain of proteus called *Proteus* X₂, or the Kingsbury strain. Some authors have proposed to classify all of the fevers of the typhus-spotted fever group into two divisions on the basis of their reaction to the Warsaw or the Kingsbury strain, but such a classification seems to us to rest on too narrow a basis.

Ross in Rhodesia has recently described a fever of the fièvre boutonneuse type that is negative for both the Warsaw and the Kingsbury strains.⁶⁹

PATHOLOGY

The morbid anatomy and histopathology of the first known disease of this group were completely worked out, according to the older standards, prior to 1910. Modern refinements of technic have, however, served to add somewhat to the pathological descriptions that had given the older known diseases a universally recognized place in general medical literature. Thus for spotted fever of the Rocky Mountains we may note the pathological studies of LeCount,⁷⁷ of Wolbach,¹¹⁹ of Reimann,¹⁸¹ and of Lillie.²²⁶ For newer additions to the histopathology of typhus fever we are chiefly indebted to Grzywo-Dabrowsky, Ceelen, Wol-

bach, Todd and Palfrey,⁴⁰ and to Da-Rocha-Lima and Montero,⁷⁵ with related work by Zinsser, Mooser, Dummer and Castaneda.^{68,80,86} The pathology described by Pinkerton and Maxcy⁸² was very probably not that of typhus but of Rocky Mountain spotted fever—eastern type.²²⁶ The older work on typhus, with additions of their own observations, was reviewed by W. Grzywo-Dabrowsky in Virchow's Archiv (ccxv, 229) for 1918, and by W. Ceelen in 1919 (Ergebn der allg Path u path Anat, xix, 1 Abt, 307).

As tsutsugamushi disease had for long been quite actively studied by opposing groups of Japanese investigators, the usual groundwork of its pathology had become well covered prior to 1925. With the introduction of the newer concepts relating to the typhus and spotted fevers, they were, by analogy, applied quickly to the study of tsutsugamushi disease by Nagayo, by Ogata and Ishiwara, and others. Their studies have not only abundantly demonstrated the rickettsial element of the disease but have served to introduce ocular and testicular inoculations as useful methods for cultivating and studying the morphology of the virus.

With regard to the newer and lesser known diseases we have to note that with respect to scarcely a one has there been an adequate beginning in the study of their morbid anatomy and histopathology. Limited exceptions may be noted with respect to fièvre boutonneuse (in which Duran I. Kuczyński and Hohenadel have recently carried out some histopathological studies) and with endemic typhus—particularly the São Paulo strain and

the strain of the southern United States^{70,78}

The lack, or virtual lack of mortality in several of the less well known diseases, and the isolating circumstances attending their locality of occurrence, have undoubtedly served to restrict the opportunities for obtaining pathological material from these diseases

Zinsser, Mooser and Castanada⁸⁰ have recently suggested the possible primitive unity of the diseases of this group

In concluding this nosologic synthesis it should again be emphasized that lack of sufficient knowledge of the lesser known diseases renders it impossible to more than approximately indicate relationship at this time. Thus, while not attempting to predict, it is warrantable to surmise that muga fever and tick-bite fever of Natal (Pretorian ten day fever) may be one and the same disease. Likewise it may be shown that Kumaun tick-typhus of India may be merely a varietal strain of *fièvre boutonneuse*. It does seem, indeed, that Schuffner's pseudo-typhus of Sumatra is merely a clinical type of Japanese-Korean flood fever, and does not deserve to be catagoried as a separate entity. Before such problems can

be solved, the clinical analysis of much larger series of the lesser known diseases will need to be made equally as well as a study of the related bacteriological and immune serum reactions. Even as to the range of vectors concerned there is much uncertainty. For example, it is possible that tick-bite fever of Natal may be transmitted by mites as well as ticks, or possibly by mites alone. And as to the vector of scrub typhus of Malasia, the acarid nature of its vector is known only as a strong possibility rather than as a certainty. Also, from unpublished observations of the author it seems that other arthropods than those mentioned are capable of inoculating man with disease of rickettsial nature. Thus a sufficiently full knowledge of the typhus-spotted fever group will not be gained until time has afforded an opportunity for correlating an abundance of observations such as those recently made by Garcia for guacarapa fever, by LaBier,¹⁵⁴ by Spencer (mentioned by Parker¹⁸⁷), by Kemp,²²³ by Toomey,²³⁰ and by Reimann²³¹ for spotted fever, and of the Italian and Greek observers concerning *fièvre boutonneuse* in the Mediterranean countries of the East.

REFERENCES

For references to the literature on the tick borne diseases consult the bibliography of subsequent article entitled "The Tick Borne Typhus-like Fevers"

¹YERSIN, A, and VASSAL, J J Typhus fever in Indo-China, *Philippine Jr Sci*, 1908, III, and *Bull soc path exot*, 1908, I, 156

²NICOLLE, C, COMTE, C, and CONSFIL, E Reproduction experimentale du typhus exanthematique chez le singe, *Compt*

rend acad sci de Paris, 1909, cxlix, July 12th

³NICOLLE, C COMTE, C, and CONSEIL, E Transmission experimentale du typhus exanthematique par le pou de corps. *Compt rend acad sci de Paris*, 1909, cxlix, 486

- ⁴RICKETTS, H T, and WILDER, R M The transmission of the typhus fever of Mexico (tabardillo) by means of the louse, *P. vestimenti*, Jr Am Med Assoc, 1910, liv, 463-467, 1304-1307
- ⁵RICKETTS, H T, and WILDER, R M The etiology of the typhus fever (tabardillo) of Mexico City, Jr Am Med Assoc, 1910, liv, 1373-1375
- ⁶GAVIÑO, A, and GIRARD, J El tifo experimental en los monos inferiores, Publ Inst Bacteriol Nac de Mexico, May and June, 1910, Aug 23, 1910, Nov 9, 1910, Nov 12, 1911
- ⁷RICKETTS, H T, and WILDER, R M Further investigations regarding the etiology of tabardillo, Mexican typhus fever Jr Am Med Assoc, 1910, lv, 309-311
- ⁸BRILL, N E An acute infectious disease of unknown origin A clinical study based on 221 cases, Am Jr Med Sci, 1910, cxxxix, 484-502
- ⁹ANDERSON, J F, and GOLDBERGER, J Etiology of tabardillo or Mexican typhus an experimental investigation, Jr Med Res, 1910, xxii, 469-481
- ¹⁰SMITHSON, O Mossman fever, Jr Trop Med and Hyg, 1910, vol xiii, No 12
- ¹¹NICOLLE, C, CONOR, A, and CONSEIL, E Experimental research on exanthematous typhus, Ann de l'Inst Pasteur, 1911, xxv, 97-116
- ¹²ANDERSON, J F, and GOLDBERGER, J Experimental proof of identity of Brill's disease and typhus fever, U S Pub Health Rep, 1912, xxvii, 149, and New York Med Jr, 1912, xcv, 990
- ¹³HEGLER, C, and v PROWAZEK S Fleckfieber, Berl klin Wchnschr, 1913, l, 2035-2042
- ¹⁴PLOTZ, H The etiology of typhus fever (and Brill's disease) Preliminary communication, Jr Am Med Assoc, 1914, lxii, 1556
- ¹⁵DAROCHA-LIMA, H Zur Aetiologie des Fleckfiebers, Deutsch med Wchnschr 1916, xxxvii, 1353-1354, Münch med Wchnschr, 1916, xlii, 1381-1384, 1917, lxiv, 33, 1918, lxv, 1454
- ¹⁶NICOLLE and BLAIZOT Results de la serotherapie dans le traitement du typhus exanthematique, Ann de l'Inst Pasteur, 1916, xxx, 446, and Bull de l'acad de med Paris, 1916, lxxvi, 53
- ¹⁷NOLLER, W Blut und Insektenflagellaten Zuchtung auf Platten, Arch f Schiffs- u Tropen-Hyg, 1917, xvi, 53
- ¹⁸SERGEANT, E, FOLEY, H, and VIALETTE, C Transmission a l'homme et au singe du typhus exanthematique par les poux d'un malade atteinte de fièvre recurrent et par des lentes et poux issue des précédentes Comp rend acad sci Paris, March 30, 1914, p 964, and Comp rend soc biol, 1914, lxxvii, 101
- ¹⁹SCHUFFNER, Proc Far Eastern Assoc Trop Med for 1913, 1914, 309-315
- ²⁰ESCLUSE Hemotherapie du typhus exanthematique, Press med, 1915, xxiii, 452-453
- ²¹VAUGHAN, V C History and epidemiology of typhus, Jr Am Med Assoc, 1915, lxiv, 1804-1810
- ²²PLOTZ, H, OLITZKY, P K and BAEHR, J Etiology of typhus exanthematicus, Jr Infect Dis, 1915, xii, 1-20
- ²³TOPFER, H Zur Aetiologie des "Febris Wolhynica," Berl klin Wchnschr, 1916, lxi, 323
- ²⁴WEIL and FELIX Wien klin Wchnschr, 1916, xxi, 33, 927
- ²⁵DIENES, L Das Weil-Felix'sche Bakterium, Deutsch med Wchnschr, 1917, xlii, 461-463
- ²⁶NETTER, A, and BLAIZOT Note sur quelque cas de typhus exanthematique Bull de l'acad med de Paris, 1918 lxxix 90-92
- ²⁷STRONG, R P American Red Cross Medical Research Committee report of commission on trench fever, Oxford Univ Press, 1918
- ²⁸LANDSTÄDER K and HAUSMANN, W Einige Beobachtungen über das Fleckfiebervirus, Med Klinik 1918 vii 515-518
- ²⁹DORR R and PICK R Experimentelle Untersuchungen über Infektion u

- Immunität bei Fleckfieber, Wien klin. Wchnschr, 1918, xxxi, 829-834
- ³¹MOLLERS, B., and WOLFF, G. Die bisher mit der Fleckfieberschutzimpfung gemachten Erfahrungen, Deutsch med Wchnschr, 1918, xlv, 676; and Ztschr f Hyg u Infektionskrankheit, 1919, lxxxviii, 41-65
 - ³²ARKWRIGHT, J. A.; BACOT, A., and DUNCAN, F. M. The association of rickettsia with trench fever, Jr Hyg, 1919, xviii, 76
 - ³³WEIGL, R. Studies on Rickettsia prowazeki, Przegląd Epidemiologiczny, 1920, i, 15
 - ³⁴SIKORA, H. Über die Zuchtung der Rickettsia pediculi, Arch f Schiffs- u. Tropen Hyg, 1921, xxv, 123
 - ³⁵SERGEANT, E., FOLEY, H., and VIALETTE, C. Iconologie des rickettsia signalees en 1914 chez des poux infectés de typhus exanthématique, Arch Inst Pasteur de l'Afrique du Nord, 1921, i, 215
 - ³⁶SCHULTZ, E. W. On the etiology of typhus fever, Am Jr Med Sci, 1921, clxi, 78-90
 - ³⁷BACOT, A. Probable identity of Rickettsia pediculi with Rickettsia quintana, Brit Med Jr, 1921, i, 156-157
 - ³⁸BACOT, A., and SEGAL, J. The infection of lice (*P. humanus*) with *Rickettsia prowazeki* by the injection per rectum of the blood platelets of typhus infected guinea pigs and the reinfection of other guinea pigs from these lice, Brit Jr Exp Path, 1922, iii, 125
 - ⁴⁰WOLBACH, TODD, and PALFREY. The etiology and pathology of typhus, 1922, Harvard Univ Press, also Internat Jr Pub Health, 1920, No 2, 1
 - ⁴¹ATKIN, E. E., and BACOT, A. Experiments on the infectivity of typhus virus contained in lice (*P. humanus* and *Pediculus longiceps*), Brit Jr Exp Path, 1922, iii, 196
 - ⁴²HONE, F. S. A series of cases closely resembling typhus fever, Med Jr Australia, 1922, i, 1-13
 - ⁴³KUCZYNSKI, M. H. Typhus Fieber, Med Klinik, 1922, xviii, 1579-1581
 - ⁴⁴MAXCY, K. F., and HAVENS, L. C. A series of cases giving a positive Weil-Felix reaction, Am. Jr. Trop Med, 1923, iii, 495-507.
 - ⁴⁵BRINL, F. Typhus exanthématique et le Proteus X, Arch de l'Inst. Pasteur de Tunis, 1924, xiii, 208-211.
 - ⁴⁶WHITLAND, F. T. A fever resembling a mild form of typhus, Med. Jr Australia, 1926, i, 261-266
 - ⁴⁷NICOLL, C., and CONSEIL, E. Experimental convalescents' serum in prevention of typhus, Arch de l'Inst Pasteur de Tunis, 1925, xiv, 355-383.
 - ⁴⁸FLETCHER, W., and LESSLAR, J. E. Tropical typhus, Indian Med Gaz, 1926, lxi, 529-531
 - ⁴⁹FLETCHER, W., and LESSLAR, J. E. Tropical typhus and Brill's disease, Jr Trop Med and Hyg, 1926, xxix, 374-386
 - ⁵⁰MAXCY, K. F. An epidemiological study of endemic typhus (Brill's disease) of the southern United States, U S Pub. Health Rep, 1926, xli, 2967.
 - ⁵¹MCGILLIVRAY, W. S. Typhus-like epidemics of Australia, Med Jr Australia, 1927, i, 743-744
 - ⁵²NETTER, A. Le typhus endémique bénin (maladie de Brill), Bull de l'acad de med de Paris, 1927, xcvi, 71-81
 - ⁵³NICOLLE, C., SPARROW, H., and CONSEIL, E. Vaccination preventive de l'homme contra le typhus exanthématique par inoculation répétées de petites doses de virus. Etapes et solution du problème, Arch de l'Inst Pasteur de Tunis, 1927, xvi, 1-32
 - ⁵⁴ISHIWARA, K., and OGATA, N. A contribution to the knowledge of the nature of the virus of tsutsugamushi disease Tokyo Med News, 1928, No 2581
 - ⁵⁵PINKERTON, H. Rickettsia-like organisms in scrotal sac of guinea pig with European typhus, Jr Infect Dis, 1929, xlv, 337-346
 - ⁵⁶MAXCY, K. F. Endemic typhus fever of the southern United States Reaction of the guinea pig, U S Pub. Health Rep, 1929, xlv, 589

- ⁵⁹NAGAI, M, TAMIYA, T, MITAMIRA, T, and SATO, K On the virus of tsutsugamushi disease and its demonstration by a new method, Japan Jr Exp Med, 1930, viii, 309-318
- ⁶⁰SINCLAIR, B A A possible case of tsutsugamushi or Japanese river fever occurring in the Mandated Territory of New Guinea, Med Jr of Australia, 1930, ii, 759
- ⁶¹LEWTHWAITE, R Clinical and epidemiological observations on tropical typhus in the Federated Malay States, Bull Inst Med Res Fed Malay States, 1930, No 1, 42 pp
- ⁶²LEWTHWAITE, R Experimental tropical typhus in laboratory animals, Bull Inst Med Res Fed Malay States, 1930, No 3, 10 pp
- ⁶³FLETCHER, W Typhus-like fevers of unknown etiology, with special reference to the Malay States, Proc Roy, Soc Med, 1930, xxxiii, 1021-1027
- ⁶⁴ANIGSTEIN, L Studies on tropical typhus in British Malaya (preliminary note), Malayan Med Jr, 1930, v, 62-64
- ⁶⁵MARCANDIER, and BIDEAU Note sur l'épidémiologie de la fièvre exanthématique observée à bord des navires de guerre à Toulon Rôle possible d'un acarien du rat dans la transmission, Rev de hyg et med prev, 1930, lii, 353-364
- ⁶⁶MOOSER, H, and DUMMER, C The relation of organisms in tunica vaginalis of animals inoculated with Mexican typhus to Rickettsia prowazekii and to causative agent of that disease, Jr Exp Med, 1930, li, 189-207
- ⁶⁷MARCANDIER, PLAZY, LECHUITON, and PIROT, R Transmission au singe de la fièvre exanthématique observée à bord des navires de guerre à Toulon Ses rapports avec le typhus exanthématiques, Bull de acad de med de Paris, 1931, cv, 1012-1015
- ⁶⁸MCGILLIVRAY, W S Brill's disease or pseudo-typhus, Med Jr Australia, 1931, ii, 716-719
- ⁶⁹NAGAI, M, TAMIYA, T, MITAMIRA, T, and HAZATO, H Sur le virus de typhus exanthématique, Bull Off Internat, d'Hyg pub, 1931, xxiii, 1415-1417
- ⁷⁰WOLFF, J W Enkele waarnemingen bei miptekoots en tropical typhus, Geneesk Tijdschr v Nederl-Indië, 1931, lxxvi, 35-45
- ⁷¹WOLFF, J W Observations on the Weil-Felix reaction in tsutsugamushi disease, Jr of Hygiene, 1931, xxi, 352-360
- ⁷²MONTIRO, J LEMOS Endemic typhus of São Paulo, types of typhus in America and new form in São Paulo, Brazil-med, 1931, xlv, 805-807, 1096, 1109
- ⁷³DIER, R E, RUMREICH, A, and BADGER, L F Typhus fever a virus of the typhus type derived from fleas collected from wild rats, U S Pub Health Rep, 1931, xlv, 334
- ⁷⁴DYER, R E, CEDER, E T, RUMREICH, A, and BADGER, L F Typhus fever the rat flea, *Xenopsylla cheopis*, in experimental transmission, U S Pub Health Rep, 1931, xlv, 1869-1870, 2481-2498
- ⁷⁵SHELMIRE, B, and DOVE, W E The tropical rat mite, *Liponyssus bacoti* Hirst, Jr Am Med Assoc, 1931, xcvi, 579-584
- ⁷⁶MOOSER, H, CASTANEDA, M R, and ZISSER, H Rats as carriers of Mexican typhus, Jr Am Med Assoc, 1931, xcvi, 231-232
- ⁷⁷DOVE, W E, and SHELMIRE, B Tropical rat mites, *Liponyssus bacoti* Hirst, vectors of endemic typhus, Jr Am Med Assoc, 1931, xcvi, 1506-1511
- ⁷⁸PRANKERTON, H, and MALCOLM, K F Pathological study of a case of endemic typhus in Virginia, with demonstration of rickettsia, Am Jr Path, 1931, vii, 95-104
- ⁷⁹NIGG, C, and LANDSTETTER, K Studies on cultivation of typhus fever rickettsia in presence of live tissue, Jr Exp Med, 1932, lv, 563-576
- ⁸⁰DIER, R E, WORKMAN, W G, BAILEY, L F and RUMREICH, A Experimental transmission of endemic typhus fever of United States by rat flea *Ceratophyllus fasciatus* U S Pub Health Rep 1932, lvii 931-933

- ⁸⁵DYER, R. E., WORKMAN, W. G., CEDLER, E. T.; BADGER, L. F., and RUMRIICH, A. Typhus fever multiplication of virus of endemic typhus in rat flea, *Xenopsylla cheopis*, U. S. Pub. Health Rep., 1932, xlvii, 987-995
- ⁸⁶ZINSSER, H., MOOSER, H., and CASTANIDA, M. R. Epidemiology of typhus fever and the possible evolution of the rickettsia disease group, Proc. Assoc. Am. Phys., May 3 and 4, 1932. Abstr. in Jr. Am. Med. Assoc., 1932, xcix, 70-71
- ⁸⁷SCROGGIE, F. H. Fever with some resemblance to typhus fever occurring in Port Elizabeth and District, Jr. Med. Assoc. South Africa, 1931, v, 809-814
- ⁸⁸GRAY, J. C. A note on laboratory investigations of the Port Elizabeth type of fever, Jr. Med. Assoc., South Africa, 1931, v, 814-216
- ⁸⁹ROSS, G. R. Eruptive fevers of the typhus group, with notes on a fever of the group observed in Southern Rhodesia, South Africa, Med. Jr., 1932, vi, 453-459

The Modern Hospital—Its Relationship to the Physician

By BENJAMIN W. BLACK, M.D., F.A.C.P., *Oakland, California*

THE Modern Hospital is the handmaiden of scientific medicine. It is the laboratory in which medical science is advanced and medical art perfected. In no other place have those facilities been so well assembled by which practitioners of modern medicine are able to give the patient efficient and satisfactory care. The public has learned to regard hospitals as places of hope and amelioration and to have confidence in them.

The number of hospital beds has increased several fold in the past generation in this country. The public attitude towards the care of illness in hospitals has changed during this period so that it is now unusual for patients to be cared for in any other place, even when suffering with but minor complaints. There are more than seven thousand hospitals in the United States and in them are employed six hundred fifty thousand persons who care for twelve million patients each year. With their vast investment in buildings, furnishings, and expensive equipment, hospitals have now taken their place in big business. They were first established for the care of the poor, later they were organized for the care of the rich.

The mutual interest between the hospital and the physician demands from each a more thorough appreciation of the function of the physician and his work in the hospital, and of the hospital in its effort to serve the physician, and through him the patient. Unfortunately, too little attention is given to the numerous intricate problems that enter into the day's effort and too frequently the point of view of the physician and his attitude is not understood by the hospital and the lack of sympathy accorded to the hospital does not always result in the best service to the patient with the least per capita cost. Hospitals have always performed a public service, and contrary to the opinion of many, the income from patients pays but little more than half of the necessary cost. Recently in Philadelphia it was found that fifty-nine per cent of the total hospital income came from patients, seventeen per cent from endowments, four per cent from cash contributions and seventeen per cent from other sources. This is quite typical of hospitals in most cities and it is rare when hospitals do not provide free beds for patients unable to pay. On the theory that the public supports hospitals. Because of this public support there is a feeling that hospitals are public utilities which is accentuated because of the manner of their establishment.

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In the main, the management of hospitals is in reasonably efficient hands and business-like administration characterizes their management in America. Standardized methods found in factories or automobile plants cannot well be expected. The care of a patient in a hospital still remains a special feature with its individual problems always predominating. Certain administrative principles apply to hospitals as to other business organizations, but because of the special service rendered in each case, no marked degree of standardization may be expected and successful methods used in hotel operations cannot well apply to hospital administration.

The present financial situation is one of the most distressing problems for the future of hospitals. It is my purpose to discuss with you certain items which enter into the daily work in hospitals for the purpose of presenting to your attention and intelligent understanding, some of the statements made in criticism of hospital costs and certain methods which may be inaugurated with the hope of reducing such costs and at the same time maintaining a standard of service demanded by an intelligent public and required by the physician in charge of the patient. There is an average reduction in hospital occupancy to about fifty-eight per cent of capacity with an average of forty-two per cent of the beds remaining unoccupied. This can not mean that we have too many hospital beds, nor that too liberal provisions have been made for the adequate care of the sick. Sooner or later when different conditions prevail, these empty beds will be needed; additional contributions will

make provision for a greater service to be rendered. During these periods of stress, increasing numbers of patients admitted to the hospital, who during normal times were well able to pay, have now found themselves without funds, thus creating a financial hardship on the part of the hospital to meet the cost of an essential service which cannot be eliminated. Patients, too, that were able to pay liberally for such service under different conditions now turn a most critical eye to any per capita cost which increases their hospital bill.

Industry rearranges its budget when production is curtailed and unemployment results. Curtailment in business followed by unemployment over any prolonged period of time means an increasingly greater amount of illness with increased demands to be expected upon hospital facilities. Hospitals assume an additional burden in order that the budgets in business shall balance, and even in spite of the fact that there is no known *business* reason why hospitals should assume an additional burden, it is safely predicted that they will not shirk their responsibilities towards this humane work even at the expense of great deficits. The public contributes funds for unemployment relief and provides for the victims of famine disaster and expects hospitals to carry increasing burdens at such times as these. Patients cannot be turned away because of lack of funds and the humanitarian traditions together with the support always given the hospital, requires the continuance of such service.

Hospitals are taxed in the state and communities in which they are located, as a general thing throughout this country. They have begged to be re-

lieved from such burdens where relief might be expected. They own real estate and at times receive some revenue from it, they receive endowments, the income of which is used in the main for the relief of the poor, yet there is little response found when efforts are made to have the revision of law to permit hospitals doing charitable work to become tax free. Organized hospitals throughout the country have presented their plea to legislative bodies without any marked material relief found. A much greater service could be expected to the public should this burden be no longer imposed upon them. An enlightened public conversant with these facts may be expected to be friendly to a tax free proposal if supported by those friendly to such a movement. Physicians may be expected to find a new mutual interest because of their increasingly large charitable services, knowing the difficulties confronting the hospitals and the requirements demanded for the same standards of hospital care.

Private practice now requires an investment on the part of the physician to provide a technic in handling the case never before available. This demands for his personal equipment an investment capable of reduction should he make greater use of hospital equipment thereby supplementing his service to patients. The proposal that the hospital shall supply to the practitioner many of the services that he would otherwise have to supply from private investment, is meeting with public approval and promises in its development, mutual advantages to the hospital, to the physician and to the patient. All the facilities in the hospital

ordinarily are used for the sick person demanding bed care, but for the office patient, the physician relies on his office personnel and equipment, or sends such patients to other practitioners or commercial laboratories. Should the hospital become the medical service center in the community, he has available the professional personnel and the scientific apparatus and also has contact with other physicians whose judgment or service he may need. The hospital gains through greater use of its facilities and the patient, it is felt by Dr. Rorem who advocates such a plan, would save time and expense, especially when several consultations and procedures are necessary. Were hospital equipment utilized to a greater extent by the private practitioner, an opportunity for some reduction in cost seems evident and as a rule, the hospital facilities are usually never fully utilized for inpatient care, or they may be readily expanded to absorb a much greater load. In some sections physicians are occupying offices in the hospital or in adjoining buildings with but limited office equipment required, as they utilize the facilities available in the hospital at a great advantage to themselves and to the patient they serve.

Increase in service means an increase in cost, but on the other hand, it means shortened period of hospitalization, better results, and more lives saved. During the past twenty-five years, the average stay of a patient in the hospital has been reduced nearly three fold, while the number of deaths reported are fewer in the same proportion. Whatever can be done to decrease the cost of hospital care has been done and

is being done in numerous ways, but it is unlikely that it is within the power of the hospital itself to reduce this cost to a degree beyond that which may be expected from intelligent, understanding, and full cooperation of all of those who enter into the hospital and its activities. Any hospital administrator may call attention to numerous factors that increase the cost for caring for patients. I would call your attention to certain suggestions that have come to include (a) simpler hospital plans with less expensive construction, (b) the nursing service with proposals for certain changes which are of professional interest; (c) the demand made for expensive equipment and elaborate proposals for research work, and (d) certain opportunities for savings of a minor nature having to do with the professional care of patients.

Expensive institutions require vast sums to operate. Rooms provided for private care are increasingly more elaborate and equipment necessary for efficient service is far beyond that previously supplied. Well-equipped laboratories in charge of highly skilled and expensive personnel must be prepared to do basal metabolic readings, blood chemistry examination, bacteriological, serological, physiological and biological tests as well as numerous others. Patients expect to have a certain amount of necessary service and are willing, when able, to pay for it, but the per capita cost is increased unless due regard is given for the necessity of each service.

It has been proposed that the cost of the needed hospital be reduced by constructing more cheaply with a simpler form of hospital plan. The ten-

dency now is to plan hospitals to include security for patients with studied utility so as to permit reasonably economic administration. Were construction costs reduced some of these admirable features would be lost, and the amount saved but trifling. Could a savings of as much as fifteen hundred dollars per bed be realized that would represent a savings in interest and depreciation of but one hundred eighty dollars per year, and would reflect itself in saving to the patients during a twelve day stay of but about six dollars. This, for reduction of cost to the patient offers little by way of solution.

The nursing service approximates twenty per cent of the total per capita cost and it has been charged that such service to private patients is too expensive. Many feel that the hospital should supply the necessary nursing care, but most hospitals cannot supply the care demanded and live within the income under the present system. Nursing service can no longer depend entirely upon student nurses as was once the case. Schools for nursing are in hospitals because there are patients to be cared for and they can secure this care cheaper by having training schools than they can without. If the maintenance of a training school costs the hospital more than the service of the pupil is worth, the school would no longer be a hospital problem, not because of lack of interest in education, but due to lack of money. Actual training of a student nurse rather than exploitation has been generally accepted as a requirement in the best hospital schools. On the other hand, nurses far in excess of the de-

mand are being graduated each year, many with an education entirely inadequate in competition with those better trained. Hospitals continue to run training schools as a source of profit, unless such is true, the private hospital cannot afford to operate training schools. Nursing educators are seriously applying such methods as may be at their command to eliminate schools with inferior educational standards and to encourage only those schools where training of a high standard may be available to the young woman who matriculates. The same methods are being applied for improving standards of nursing education as were applied years ago by the medical profession in its effort to improve educational standards in medical schools.

Nursing schools of a high standard must receive sufficient financial support to maintain full time instructors and to allow students sufficient periods for class work and hours for study. Maids are provided in many hospitals to perform numerous household duties, in the past performed by students. This also requires the employment of more graduate nurses which has increased the cost enormously and one may confidently expect that the cost of hospital nursing service will increase rather than decrease. An active interest on the part of nursing educators seems to point to a new plan of nursing education, the laboratory work and the teaching of basic sciences carried on as a part of the public school system in junior colleges or universities, requiring of the hospital only the bedside teaching. This would permit student nurses to provide a service comparable to that supplied by graduates and at

the same time would place the responsibility of the basic scientific education on the school system, thus relieving hospitals maintaining good schools of this financial burden.

The charge for graduate nursing service is not excessive. The acceptable graduate must be well prepared and have devoted years in preparation, after a reasonable basic education. She works under very trying conditions and on the average she is employed but about twenty-two days per month, and, during the entire time she must maintain a home as do other employed persons. Her income is about fifteen hundred dollars or less annually, hardly comparable under normal conditions to many employed with much less preparation. Her services are indispensable, her active years are short, and were it not for the satisfaction that comes from giving an altruistic service she would not seek to remain in this field.

Special nurses are often employed unnecessarily and their services constitute a severe financial drain and increase the per capita cost in a manner that might be avoided if they were employed only because of the professional requirement of the patient. The National Committee on Nursing Education in a survey made on the need of supplying special nurses, studied 1892 cases in which special nurses had been employed. This report states that the doctor in charge of the case urged a special nurse in but forty per cent of these cases, in thirty-three per cent a special nurse was ordered because the family desired a better service than that supplied by the hospital, in twenty-two per cent the patient demanded the special nurse because she felt that

the nursing service was inadequate; the hospital suggested a special nurse in but three per cent of the cases and in two per cent a special nurse was provided for no reason except that friends of the patient who had enjoyed hospital care had been so provided.

A perfectly legitimate subject for discussion is just what constitutes adequate nursing care. The hospital must provide a service to cover reasonable demands, but that service which requires an additional burden for the hospital to carry, without materially meeting the real professional needs of the patient, should not add to the burden of per capita cost. The patient's feelings must enter into any consideration of the subject. An agreement between the physician, the hospital and the patient, or her family, will at frequent intervals partially or entirely eliminate the demand for special nurses, when she is employed only to satisfy the unreasonable whims of someone. The charges for her services, when demanded for no good professional reason mount with increasing criticism as a charge against the hospital when the institution is an innocent victim of a situation which develops without profit to it and with no need on the part of the patient. A necessary nursing service should be demanded, but patients require protection in this hour of need against the necessity for paying for a special nurse when such care is not required.

The advancement of medical science through research is generally accepted as a proper function of a modern hospital. The goal of such activity requires that we increase our effective knowledge in the interest of the pa-

tient and his prompt recovery. Due to advancements made through clinical research, miracles in the treatment of disease come daily within the experience of all of us. When properly conducted and supervised, research promotes understanding of the underlying mechanism of disease and furnishes a better background for diagnosis and treatment. Clinical research stimulates better work on the part of the staff as it engenders an inquiring frame of mind. Generally it is recognized that effective clinical research can be carried out only in the hospital.

The proper use of material already provided will supply a satisfactory basis for clinical studies not now used to full advantage. As most of the elements required in any research problem are usually supplied by the hospital itself, it would follow that a greater use might be made of the facilities found available in any well organized institution. Well kept records include a thorough history, the results of physical examination, and the usual laboratory studies on all patients admitted. Such records, while of value during the time the patient is under immediate care, become of increasingly greater value when they are effectively used as a basis for study and to draw conclusions from a series of cases treated. Records should be made easily accessible to any member of the staff who desires to make a study of a series of cases and the record room may prove to be the incentive for conducting numerous further studies. A variety of clinical problems yet to be solved may be approached with no expense involved when effective use is made of the material already at hand. Such a

program would have the aggressive support of any hospital administration because of the actual accomplishment in better diagnosis and treatment, and the stimulation towards the completion of better and more complete records. Any program mutually arranged would provide for the beginnings of clinical study, complete records easily accessible have effective use.

Scientific enthusiasm is always a laudable quality in any member of the staff but it is not conducive to economy. Dr. Follansbee believes that, "the interesting case is an invitation to use all known tests applicable to it as a check against the reported findings of others. The repetition of such tests during the hospital stay of the patient and the agreement of such tests with expected results are sources of intense satisfaction to the physician who has ordered such tests. The justification however for making repeated tests of no particular importance except to satisfy the clinician is in raising the standards of medical inquiry and tending to stimulate additional studies which apply to patients suffering with similar disease, but repeated tests of such character can hardly be justified on any other ground." A comparison of numerous "interesting cases" where expensive laboratory investigations and other procedures have been carried out might point the way for standardized procedures, modified only as the problem changes, and provide an end result which justifies such an expensive program.

Without any desire to give offense, I desire to refer to certain extravagances of visiting physicians which add to the per capita cost. Care here might result

in a savings covering numerous minor items which accumulate over a period of years and tend to increase the cost of care to the patient or to the hospital. There are savings that may be made in the professional care without harm to the patient. They may not be large nor impressive, but to the patients who have difficulty in making payment for the expensive necessary service, they will be appreciated and where payment is not made by the patient, the cost to the hospital is material. According to Dr. Follansbee, "there are times when all the diagnostic facilities of the hospital and the acumen of the staff are insufficient to make a diagnosis but there are other times when the diagnosis is so evident that expensive diagnostic procedures can merely be confirmative of what is already known. It is therefore an extravagant and unnecessary cost. A patient suffering from typical gallstone colic with a history of repeated attacks but otherwise normal on physical examination, needs no intravenous dye or X-ray examination to make the proper diagnosis." Internes require that hospital facilities shall be available in order that they may be taught all that a hospital can teach. It is questionable whether they would not learn more and be more self-reliant if the scientific laboratory were displaced in cases such as the one mentioned, by the more consuming teaching of the art of history taking and physical examining and the conclusions to be reached thereby.

With the lure of modern advertising in the field of new preparations, physicians are confronted with a multitude of patented, copyrighted and proprietary remedies. The art of pre-scrib-

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in a savings covering numerous minor items which accumulate over a period of years and tend to increase the cost of care to the patient or to the hospital. There are savings that may be made in the professional care without harm to the patient. They may not be large nor impressive, but to the patients who have difficulty in making payment for the expensive necessary service, they will be appreciated and where payment is not made by the patient, the cost to the hospital is material. According to Dr. Follansbee, "there are times when all the diagnostic facilities of the hospital and the acumen of the staff are insufficient to make a diagnosis but there are other times when the diagnosis is so evident that expensive diagnostic procedures can merely be confirmative of what is already known. It is therefore, an extravagant and unnecessary cost. A patient suffering from typical gallstone colic with a history of repeated attacks but otherwise normal on physical examination, needs no intravenous dye or X-ray examination to make the proper diagnosis." Internes require that hospital facilities shall be available in order that they may be taught all that a hospital can teach. It is questionable whether they would not learn more and be more self-reliant if the scientific laboratory were displaced in cases such as the one mentioned, by the more consuming teaching of the art of history taking and physical examining and the conclusions to be reached thereby.

With the lure of modern advertising in the field of new preparations, physicians are confronted with a multitude of patented, copyrighted and proprietary remedies. The art of prescribing

the nursing service was inadequate; the hospital suggested a special nurse in but three per cent of the cases and in two per cent a special nurse was provided for no reason except that friends of the patient who had enjoyed hospital care had been so provided

A perfectly legitimate subject for discussion is just what constitutes adequate nursing care. The hospital must provide a service to cover reasonable demands, but that service which requires an additional burden for the hospital to carry, without materially meeting the real professional needs of the patient, should not add to the burden of per capita cost. The patient's feelings must enter into any consideration of the subject. An agreement between the physician, the hospital and the patient, or her family, will at frequent intervals partially or entirely eliminate the demand for special nurses, when she is employed only to satisfy the unreasonable whims of someone. The charges for her services, when demanded for no good professional reason mount with increasing criticism as a charge against the hospital when the institution is an innocent victim of a situation which develops without profit to it and with no need on the part of the patient. A necessary nursing service should be demanded, but patients require protection in this hour of need against the necessity for paying for a special nurse when such care is not required.

The advancement of medical science through research is generally accepted as a proper function of a modern hospital. The goal of such activity requires that we increase our effective knowledge in the interest of the pa-

tient and his prompt recovery. Due to advancements made through clinical research, miracles in the treatment of disease come daily within the experience of all of us. When properly conducted and supervised, research promotes understanding of the underlying mechanism of disease and furnishes a better background for diagnosis and treatment. Clinical research stimulates better work on the part of the staff as it engenders an inquiring frame of mind. Generally it is recognized that effective clinical research can be carried out only in the hospital.

The proper use of material already provided will supply a satisfactory basis for clinical studies not now used to full advantage. As most of the elements required in any research problem are usually supplied by the hospital itself, it would follow that a greater use might be made of the facilities found available in any well organized institution. Well kept records include a thorough history, the results of physical examination, and the usual laboratory studies on all patients admitted. Such records, while of value during the time the patient is under immediate care, become of increasingly greater value when they are effectively used as a basis for study and to draw conclusions from a series of cases treated. Records should be made easily accessible to any member of the staff who desires to make a study of a series of cases and the record room may prove to be the incentive for conducting numerous further studies. A variety of clinical problems yet to be solved may be approached with no expense involved when effective use is made of the material already at hand. Such a

program would have the aggressive support of any hospital administration because of the actual accomplishment in better diagnosis and treatment, and the stimulation towards the completion of better and more complete records. Any program mutually arranged would provide for the beginnings of clinical study, complete records easily accessible have effective use.

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ing has almost gone out of fashion with the advent of detail men and their willingness to serve in providing stock preparations sold under attractive titles. Such remedies when they appear on the market are several times more expensive and no more effective than remedies available in the United States Pharmacopeia. Recently a comparison was made in a very well organized hospital to determine the comparative cost of drugs and standard preparations listed, with similar proprietary preparations used because of the demand made by the staff and others concerned. It was found that a cost approximately four times greater on the average was carried by the hospital for proprietary remedies supplied as against the standard preparations that might replace them. In another hospital with a three thousand dollar stock of standard preparations with no proprietaries listed, the cost of drugs per patient with an acute condition totals sixty-seven cents. Twenty-two cents of this was paid for biologics and but forty-five cents covered the necessary required medications. Attention to the remedies prescribed, the standards used and the copyrighted names found on the shelves in any hospital pharmacy, will be of sufficient interest to the hospital and the physician to justify a further study.

Routine prescribing of costly hypnotics and sedatives night after night simply to satisfy a patient's whim is expensive and vicious. Barbitol and similar hypnotics are not habit forming drugs, but there is such a thing as a habit of not sleeping without the drug which develops in certain classes of patients. Morphine sulphate is giv-

en much too frequently in many hospitals, particularly those of the public type. It is quite possible without any injury to the patient to reduce the use of the morphine and its derivatives very materially with beneficial results to the patients and a decreasing cost for unnecessary expenditures. In one hospital with a very large emergency and surgical service handling patients with acute illnesses the total morphine use averages but six and one-half grains per day. There is a deplorable waste of dressings, particularly in the accident service of any hospital. The house staff may be taught economy in the use of gauze, bandages, dressings, adhesive and in the use of drugs for routine prescribing. One-half the amount of bandage ordinarily used, if properly applied, will hold the dressing in place better than twice the amount improperly applied. The hospital should supply abdominal pads of sufficient size only and dressings should be adopted for use to the type of case at hand. These are matters of economical practice that demand our mutual interest. Team work between the hospital administration and the staff is dependent upon the personality of one leader—enthusiasm, patience, fairness, generosity and tact can develop team work and do wonders in any institution. Such a leader in a hospital is usually the superintendent and he may be either a layman or a professional man. If he presents the right qualifications he will attract the various divisions engaged in hospital work and establish a well-functioning machine. The small extravagances which have been mentioned, as well as many others, which enter into increased per capita cost can

be decreased and often times entirely eliminated if the superintendent will apply his qualities of leadership and the visiting staff will pride themselves on their ability to effectively treat the patient, demanding only the necessary service and requiring for the patient no extravagances which may be eliminated

There are many other problems which demand our attention but which may be only mentioned as a basis for mutual interest between the physician and the hospital. Hospitals are unjustly criticized because of the increasing costs and many times with no responsibility whatsoever. The entire cost of medical care including professional services rendered by the physician, the care of the patient in the hospital and the ability of people of moderate means to pay for such services continue to challenge the best efforts of trained investigators in this field. As physicians interested in hospitals, we are confronted with the demand to supply to every person the necessary medical care at a cost within the power of the ordinary citizen to pay. Judge Rosen of New Orleans has said that, "This great and rich nation is not likely to rest content until its citizens the country over receive the best possible care. To meet the tremendous problems of distributing medical service to a hundred million people, it is clearly evident that charitable gifts will not suffice. Either the state will have to take the responsibility, or representatives of the general public must

unite to find the best methods whereby people will get good medical care at a fair price."

Medical practice both in the hospital and at home is definitely passing through a crisis from which it may be assumed that marked changes will require a readaptation to the times. From an editorial appearing in the March, 1932, *ANNALS OF INTERNAL MEDICINE*, I would conclude by quoting "It is a time for those who, by reason of official position or by reason of unusual ability, are the leaders of our profession to put their minds together and help us to chart our course. It is not the time for reactionary impulsive action, impractical experiments, or challenging attitudes. We must be on guard against impractical panaceas which come either from within or from without the profession, and hope that no such panaceas will obtain legislative approval.

"It is not unlikely that there is to be a distinct change in the character and type of medical practice in the next generation. A variety of social movements affecting medicine are under way, and their development is not to be stopped. State medicine is edging its way in and is not to be entirely kept out. That concessions must be made, compromises accepted must be recognized by the rank and file of the profession. It will be the obligation of our leaders to guide, so far as they may, these movements, and to advise us when such concessions are necessary and compromises essential."



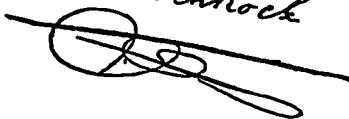
Anton van Leeuwenhoek


FIG 1

Antony van Leeuwenhoek

1632-1723

By CARL V WELLER, M S , M D , F A C P , *Ann Arbor, Michigan*

ANTONY van Leeuwenhoek was born in the old Dutch city of Delft, on October 24th, 1632. For a number of years both before and after that memorable date, events of prime importance were occurring in the awakening scientific world. In that year William Harvey was fifty-four years old, and four years before that date Harvey had written in the dedication of his *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, addressing the President and members of the Royal College of Physicians "I have already and repeatedly presented you my learned friends, with my new views of the motion and function of the heart, in my anatomical lectures, but having now for more than nine years confirmed these views by multiplied demonstrations in your presence, illustrated them by arguments, and freed them from the objections of the most learned and skillful anatomists, I at length yield to the requests, I might say entreaties, of many, and here present them for general consideration in this treatise

"* * * * * And as this book alone declares the blood to course and evolve by a new route, very different from the

ancient and beaten pathway trodden for so many ages, and illustrated by such a host of learned and distinguished men, I was greatly afraid lest I might be charged with presumption did I lay my work before the public at home, or send it beyond seas for impression, unless I had first proposed the subject to you, had confirmed its conclusions by ocular demonstrations in your presence, had replied to your doubts and objections, and secured the assent and support of our distinguished President." And thus, in 1628, was the truth in regard to the motion of the blood, a circular motion, made known.

While Leeuwenhoek was yet a boy in his early teens, an interesting research club was in process of birth in Oxford. Wearied of arguments on religion, on state affairs and on the then current economic depression, a group of young men (their average age was but thirty-four) were holding weekly meetings, "sometimes at Dr Goddard's lodgings, sometimes at the Mitre in Wood Street hard by," or at Dr Petty's lodgings "because of the conveniences we had there (being the house of an apothecary) to view, and make use of, drugs and other like matters as there was occasion." A common interest in Natural Philosophy

Presented at the Combined Memorial Meeting of the Research Clubs of the University of Michigan 1932



Anton van Leeuwenhoek

[Signature]

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and a conviction that the truth was to be found by going to Nature and not in man-made canons bound this group together. John Wallis, later a mathematician of note, wrote that they confined themselves "to philosophical inquiries, and such as related thereunto; as Physick, Anatomy, Geometry, Astronomy, Navigation, Staticks, Mechanicks, and Natural Experiments." Those interested in medical matters must have influenced decidedly the complexion of the entire group. With Robert Boyle, Robert Hooke, Seth Ward and Matthew Wren, there were to be found among the medical group, the young anatomist, Christopher Wren, Thomas Willis, who was already interested in the brain and nervous system, Jonathan Goddard, whose name became coupled with his remedy, Goddard's drops, Francis Glisson, after whom the capsule of the liver is named, George Ent, intimate friend and executor of Harvey, Charles Scarbrough, who was to attend Charles II in his last illness, William Petty, who was Cromwell's First Physician to the Army in Ireland, and Christopher Merritt, who became the first custodian of the medical library which Harvey gave to the College of Physicians.

About 1658, the meetings of this research club ceased to be held in Oxford, for a number of its members had then moved to London, and, in 1662, Charles II bestowed upon the organization a royal charter. Such was the conception and nativity of The Royal Society of London.

Samuel Pepys, the diarist, happened to be present at Whitehall on January 9, 1665, when The Royal Society received this charter, the King signing

as 'Founder' and James, the Duke of York, as 'Fellow'. Pepys wrote as a part of his entry for that date "Up and walked to Whitehall, it still being a brave frost, and I in perfect good health, blessed be God! In my way saw a woman that broke her thigh, in her heels slipping up with the frosty street To the Duke, and there did our usual work. Here I saw The Royal Society bring their new book, wherein is nobly writ their charter and laws, and comes to be signed by the Duke of York as a Fellow, and all the Fellows' hands are to be entered there, and he as a monument; and the King hath put his with the word Founder."

The Curator of Experiments to The Royal Society during this period was Robert Hooke. Interested in all things mechanical, he was the inventive genius of his age. He, himself, estimated his inventions at not fewer than a thousand. He was particularly interested in microscopy, and in 1665, only three years after The Royal Society had received its charter, Hooke published his *Micrographia or Some Physiological Descriptions of Minute Bodies Made by Magnifying Glasses With Observations and Inquiries Thereupon*. In this book he applied the name "cells" to the structure of cork. This marks the beginning of knowledge of the cellular structure of living things. Hooke used a condensing system for increasing the light upon the object under investigation, and, according to his own account, his microscope had two or three lenses. Yet he recognized the fact that the simpler the optical system the better the illumination and definition, for he wrote "But whenever I had occasion to ex-

amine the small parts of a Body more accurately, I took out the middle Glass, and only made use of one Eye Glass with the Object Glass, for always the fewer the refractions are, the more bright and clear the Object appears. And therefore, 'tis not to be doubted, but could we make a Microscope to have only one refraction, it would, *ceteris paribus*, far excel any other that had a greater number." At that very time just such microscopes as Hooke coveted were being made in Delft by the young Dutchman, then 33 years old, whose tercentenary we celebrate! To him we must now turn our attention.

Descended from a long line of Delft brewers, upon the death of his father, Philip Antony van Leeuwenhoek, the young Antony was sent away to school at Warmond, and later to Benthuisen where he was under the care of an uncle who then held some official position. Presumably it was planned to have him follow his uncle's career as an officeholder, but at the age of sixteen years he was put into a clothier's establishment in Amsterdam where he made use of his special aptitude in elementary mathematics as bookkeeper and cashier. His work in the draper's shop could not have continued for more than five or six years, for, at the age of twenty-two, he had returned to Delft and was married. Six years later he secured appointment to the position of "Chamberlain of the Sheriff" of Delft. His commission is still in existence and in it his duties are clearly set forth. Wynter-Blyth translated them as follows: "To open and shut the door of the chamber, both on ordinary and extraordinary days of

meeting; to show honor and respect to the councillors, to keep inviolate anything he might hear in the council chamber, to keep the chamber clean, to make the fires, also to preserve the place from fire, and to do all that a good and faithful chamberlain should do." In short, Antony van Leeuwenhoek was made janitor of the town hall. This appointment gave him a small, but certain, income. He held this position for thirty-nine years and the salary was paid him until his death. As Wynter-Blyth puts it, just "as the Scots made their greatest poet an exciseman, so the Dutch made their philosopher a beadle."

For Leeuwenhoek, and for the broadening stream of scientific knowledge, this official appointment was of the greatest advantage. It permitted him to earn his living in about as simple and non-time-consuming a manner as could well be imagined. We must believe that he attended to those simple duties honestly and well, but they could not have engaged more than a small fraction of his time. At just what period he commenced to construct microscopes and to make observations with them is not known, but it was certainly a number of years before 1673 when, at the age of 41 years, he was first introduced to The Royal Society of London by Reimer de Graaf. This first communication can be found on page 6037, Volume VIII, of the *Philosophical Transactions* and it bears the title "A specimen of some observations made by a Microscope contrived by Mr Leeuwenhoek, concerning Mould upon the skin, flesh, etc., the Sting of a Bee, etc." From that time on, as will appear, the Dutch

microscopist became a frequent contributor

For Leeuwenhoek, a new exploration in the realm of the sub-visual meant first the construction of a new microscope, for so inconvenient and limited were the means provided for bringing the object to be observed into proper relationship to the lens that to a certain extent each instrument was constructed to serve a special purpose. These microscopes, which might better be called magnifying glasses, Leeuwenhoek built entirely with his own hands

not simply a polished spherical globule of glass such as others had used, securely held between two plates. These were joined by several small rivets or screws, placed near the margin. The plates were of silver, gold or brass, and were pierced by a small opening, corresponding to the position of the lens. Attached to these plates there was a small object table borne upon a movable screw and carrying also a smaller adjustable object holder to retain and move the object under examination (Figure 2.)

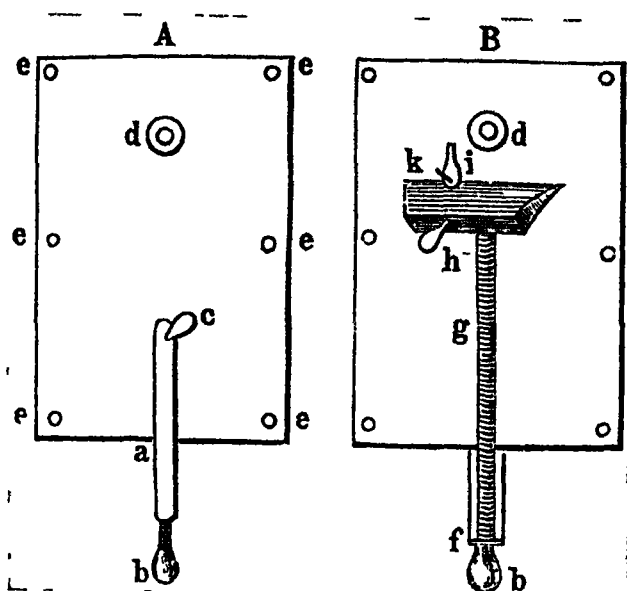


FIG. 2 Front and back views of a Leeuwenhoek microscope. The double convex lens is in position at *d*. At the points marked *e* are six screws or rivets for holding the two metal plates together. The handle, *a*, carries also a threaded screw, *g*, for varying the height of the object carrier, *k*. This, in turn, bears the object holder, *i*, with arrangements for altering the position of the object.

For some of them he even extracted the silver from the ore himself. The lenses he likewise formed and polished, and therein lay his special skill.

From his own descriptions, and from drawings prepared by others, it is known that practically all of the microscopes made by Leeuwenhoek consisted of a very small double convex lens,

Our knowledge of the microscopes made by Leeuwenhoek comes largely from two sources. He bequeathed twenty-six of them to The Royal Society, and these, although no longer known to exist, were described and illustrated by Baker in his book *Employment for the Microscope*, London, 1753. At a visual distance of eight

inches from the lens, these gave magnifications ranging from 40 to 160 times. However, a Leeuwenhoek microscope in Utrecht was found to magnify 270 fold.

Harting described the auction catalogue of Leeuwenhoek's microscopes as they were put up for sale on May 29, 1747. In this catalogue it is set forth that Leeuwenhoek left no less than 247 complete microscopes, many with an object to be viewed still in position, also 172 additional lenses mounted between plates, a total of 419 lenses. Three of these lenses were of rock crystal (*Amersfoorte Diamanten*). Two microscopes were said to have two lenses and one three, from which it has been assumed that Leeuwenhoek made use of doublet and triplet lenses. It is probable, however, that these were instruments with two and three simple lenses mounted at as many separate openings. Of the group included in this sale, 160 had silver plates for mounting the lens, and three had plates of gold. The remainder were of brass. The catalogue gave the names of the purchasers, who were all Dutch. Yet, in 1858, Harting commented upon the extreme scarcity of van Leeuwenhoek microscopes in Holland. (This should furnish the basis for an intriguing quest for the collector.)

Although Hooke made use of a condensing system in order to increase the illumination of the object, there is no evidence that Leeuwenhoek employed such a device. His microscopes were made to be held in the hand, directed toward the source of light. In 1689, however, he described for The Royal Society a perforated mirror with a lens

at the orifice which would increase the amount of light incident upon the object which was being viewed.

With such instruments as these, Leeuwenhoek examined, described and drew those natural objects which attracted his interest and for which he could devise the means of inspection through his magnifiers. Sometimes special apparatus had to be contrived for holding immobile, and yet alive, such material as tadpoles and eels. For observation of the circulation he used a special stand provided with perforated plates for the insertion of glass tubes to contain the living subject. The auction catalogue to which reference has already been made listed eight such special stands of silver and four of brass. An illustrator of some fifty years ago has supplied the tube and its imprisoned occupant, and this apparatus has been reconstructed in facsimile.

The objects chosen by this adventurer in the unknown were of the most diverse nature. The sequence of his investigations seems to indicate a lack of any systematic pursuit. Yet we must bear in mind that Leeuwenhoek was driven by dynamic curiosity, for he was viewing that which never before had been seen by the human eye. It mattered not whether the object of his inspection might be inanimate or animate, animal or vegetable, native or the gift of some merchant returning from a distant land, if it did but offer an as yet unknown morphology awaiting description. For human authority he cared not at all. The views of his predecessors seldom concerned him, but he sought truth in Nature, and if others denied the accuracy of his observa-

tions, Nature was again the court to which to appeal.

Thus we find among the subjects investigated by Leeuwenhoek an extraordinary variety. The lists compiled by Richardson are sufficiently complete to indicate the range, and I follow his grouping in part.

Animals of different kinds. Animalcules in water of various sorts and in infusions, the ant, cantharides; cochineal, various fish, the flea, the fly, the frog; the liver fluke of sheep; the gnat, locust; louse, maggots, millipeds, mites; sea and fresh-water muscels, the scorpion, shrimp; silkworm; snails; spiders; tadpoles; the viper, and its poison; the weevil, or corn beetle; and the whale.

Special structures and functions of animals. Acids in the stomach, and their part in digestion, the blood, its globules, its minute circulation, its coagulation, and the frequency of its course from the heart; the structure of bones, the brain of various animals; the eye and its crystalline lens; the visual organs in the eyes of the silkworm moth, of a beetle and of a shrimp, the optic nerves of the fly; feathers of birds and the scales of insects, muscle fibers; the generation of animals, with refutation of spontaneous generation, the spermatozoa of many species; hair; the structure of the heart in various species, the intestines, their membranes and vessels, the structure of nerves; epithelial cells of the lining membrane of the mouth; the structure of the spleen; and the coating upon the tongue in fevers.

The structure of plants and of vegetable products: The ash tree; the beech, ebony, wood, elm timber; fir

timber, willow, boxwood; the barks of various trees; the cocoa tree and nut, coffee; corn stored in granaries, cotton; the structure and production of oak galls; excrescences on thistles and on willow leaves, the hop, the lime tree; various spices, including mace, pepper, nutmeg, and sage; the nettle; the root of pareira brava; Peruvian bark, peat, the periwinkle; rushes and their formation, the seeds of various trees and plants, including tobacco; the nature and properties of tea, vinegar, and wheat.

It is evident that there are but few fields of modern microscopical investigation in which the researcher need not have knowledge of the work of Leeuwenhoek if he would know the firstlings of his subject. Yet Leeuwenhoek was an uneducated man. Aside from his knowledge of elementary mathematics his experiences at school had little or no influence upon his work. He spoke, read and wrote Dutch, but he knew no other language. Neither did he travel. There is no indication that he ever addressed a scientific society or in any manner set forth his discoveries in public address. Yet as his fame grew, he was visited by his contemporaries in scientific investigation and by various royal personages, including Peter the Great of Russia and Queen Mary of England. To Queen Mary he gave a pair of his microscopes of the same sort as those which he later devised to The Royal Society, of which, in 1680, he had been elected a Fellow (not a Corresponding Member as is sometimes stated). He never attended a meeting of The Royal Society and yet became its most prolific contributor. To it his discov-

eries were imparted by letters, perhaps as many as three hundred and seventy-five communications in all, including the various lesser explanatory notes and answers to queries. The French Academy of Sciences, of which he was elected a Corresponding Member in 1697, received twenty-six letters, and still others were written to individuals. While Leeuwenhoek was yet living, collections of his letters appeared from time to time but there were some which were not included in such compilations. In 1798-1801, Samuel Hoole published a two volume collection of the letters of Leeuwenhoek, consisting of selections concerning over one hundred and fifty topics. All reference to the male reproductive cells and to the generation of animals, comprising the most numerous and probably the most valuable group of papers was omitted, apparently on the ground of indelicacy.

The temptation to quote extensively from the letters of Leeuwenhoek is indeed great, but only a few selections can be made. Unfortunately, some of the simple homely quality of the original Dutch is lost in the translations.

COCHINEAL

Leeuwenhoek had communicated to The Royal Society in 1691, an account of the mode of preparation of cochineal grains, as he had had it from an old Spaniard who had lived many years in the West Indies. In 1704, he examined this dye stuff microscopically, and reported his findings in a long letter from which the following are excerpts.

"A merchant of Amsterdam writes, that it is impossible, and altogether incredible that the drug called cochineal should be,

as I have asserted, flies, or any sort of animal endued with wings, head or feet, not only if we consider the vast number of them that are brought in every fleet from America, for you will find that two of the largest of these particles, eight of the middling sort, and twenty of the smallest, scarcely weigh a gold grain, so that in a pound of them, at a medium of large and small, one may count 102,400 particles, now in a fleet that brings 200,000 pounds of this drug, what a vast number of animals there must be? Besides, says he, where can you find men enough, who at the proper time of the year shall catch these insects, and dismember every individual by pulling off its head, legs and wings, etc., so that he concludes that cochineal must needs be a fruit, or the excrescence of some kind of plant.

"Though I am convinced that cochineal is nothing else but the trunk or hinder part of a living creature, and was persuaded also that the cochineal animals, like other insects from worms, are changed into flies, yet for further satisfaction, I have renewed my inquiries upon this subject, and in so doing I find reason to reject some of my former positions, being now fully convinced that the cochineal animals are not produced from worms, but at once bring forth their own likeness.

* * * * *

"Now for further satisfaction, I took several particles of this same cochineal, [figure 3] both of the largest and smallest, and having dissected them, I found that they had all eggs in their bellies, excepting only one that was exceeding small. Having opened some of the largest trunks, and separated the eggs, which I took out of their bodies, and counted them, I judged that there were above 200, and having observed several of them with my microscope, I could perceive not only a membrane or shell on most of them, but also an animalculum of an oval shape included in the said shell, and almost as large as the shell that contained it, which seemed at first very surprising, and almost incredible in so small a species of fly as the cochineal, till by a very nice and long inquiry I was fully satisfied, that it was really an animalculum that lay within it. I pursued this operation with so good success,

that I not only separated the egg-shell from the animalculum but in some of them I could perceive their legs also orderly folded up against their body, and could separate them from it, especially in such as were full grown, nay, in some I even discovered the several joints of the legs, and thus in the space of two days I saw the legs of 100 animalcula, many of which in my handling were broken off, and lay by themselves"

DESCRIPTION OF A LOUSE FEEDING 1674

"Having formerly spoken of the louse, her sting, etc, I cannot here omit to say something of what I have seen within that creature I have several times put a hungry louse upon my hand, to observe her drawing blood from thence, and the subsequent motion of her body which was thus The louse having fixed her sting in the skin, and now drawing blood, the blood passes to the fore part of the head in a fine stream, and then it falls into a larger round place, which I take to be filled with air This large room being, as to its fore part, filled about half full with blood, then propels its blood backward, and the air forward again, and this is continued with great quickness, while the louse is drawing the blood, except that at times she stops a little, as if she were

tired and recollects herself, a motion like that, it seems, which is in the mouth of a sucking infant from thence the blood passes in a fine stream into the midst of her head, that being also a large round place, where it has the same motion Hence it passes in a subtile stream to the breast, and thence into a gut, which goes to the hindmost part of the body, and with a curvity bends a little upwards again In the breast and gut the blood is, without intermission, moved with great force, and especially in the gut; and that with such strong beatings downward, and with such a retrocourse and contraction of the gut, that a curious eye cannot but admire that motion In the upper part of the crooked ascending gut, which is very straight [i.e., narrow], now and then a little blood crowds through, which returns not back, and here I presume is a little valve the blood, that is thrust through here, stands still, and soon receives another nature, becoming of a watery colour, and in this watery liquor there appear some blackish sandy particles, having a confused motion, which grow in size and being grown as large as sand is to our eye, the said particles join themselves close and firm together, as it were in one mass, and then shoot down to the anus, carrying with them, in case the louse have much

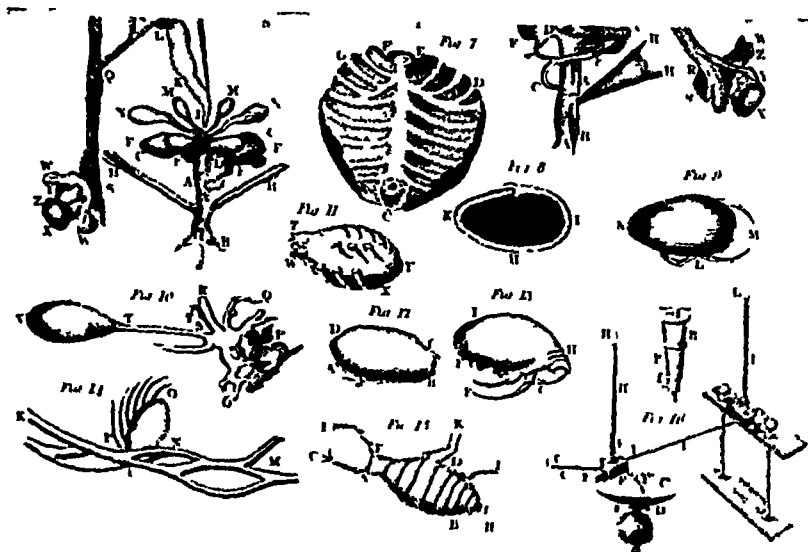


FIG. 3 Drawings by Leeuwenhoek to illustrate the anatomy of the cochineal insect. Figures 7 to 15 deal with this subject, all except the first showing stages of the embryos which he found in the body of the adult female

blood in her body, a little aqueous blood. These excreted particles appear like the excrement of a silk-worm."

THE FIRST PROTOZOOLOGY AND THE FIRST BACTERIOLOGY

Dobell wrote of Leeuwenhoek as the first of the protozoologists and expressed himself as fully satisfied that no successful effort had ever been made to refute that contention. In the minute living things which he discovered in so many homely sources, Leeuwenhoek evidently took great delight. He designated them by terms which can be translated 'little animals', 'beasties', or 'little creatures', as if he had a tender feeling towards them. Perhaps he felt the fundamental biological unity of all living things. At any rate, he reasoned that even the smallest of them must have an internal morphological organization like that of the larger animals. Thus he was led to speculate, with detailed mathematical calculations, upon such hypothetical possibilities as the probable size of the blood capillaries in minute unicellular organisms.

I select for quotation here Leeuwenhoek's description of one of the minute forms of life which, in 1675, he saw "in rain water, which had stood but a few days in a new earthen pot, glazed blue within." This is the first description of *Vorticella*. An abridged version of this letter appears in the *Philosophical Transactions of The Royal Society* for 1677, but I use Dobell's translation which not only is more complete but also strives to catch the flavor of the original Dutch.

"Of the first sort of creatures that I discovered in this water, I saw, after divers observations, that the bodies consisted of

5, 6, 7, or 8 very clear globules, but without being able to discern any membrane or skin that held these globules together, or in which they were inclosed. When these little animals moved themselves, they sometimes stuck out two little horns [optical section of the wreath of cilia round the peristome], which were continually moved, after the fashion of a horse's ears. The part between these little horns was flat, their body else being roundish, save only that it ran somewhat to a point at the hinder end, at which end it had a tail, near four times as long as the whole body, and looking as thick, when viewed through my microscope, as a spider's web. At the end of this tail there was a pellet, of the bigness of one of the globules of the body, and this tail I could not perceive to be used by them for their movements in very clear water. These little animals were the most wretched creatures that I have ever seen, for when, with the pellet, they did but encounter any particles or little filaments (of which there are many in water, especially if it hath but stood some days), they stuck entangled in them, and then stretched their body into an oval, and did struggle, by strongly extending themselves, to get their tail loose, whereby their whole body then sprang back toward the pellet of the tail, and their tails then coiled up serpent-wise, after the fashion of a copper or iron wire that, having been wound close about a round stick, and then taken off, retains all its windings. This motion of extension and contraction of the tail continued, and I have seen several hundred of these little animals, caught fast by one another in a few filaments, lying within the compass of a coarse grain of sand."

In the same letter Leeuwenhoek wrote of other sorts of living creatures which were so small that he was not able to give them a definite figure. The larger forms he demonstrated to spectators, but of the smallest he wrote that they were not seen by others for he saw them by another microscope which he reserved for himself alone. These smallest forms were probably bacteria.

Then, in 1684, he wrote to The Royal Society as follows

"Though my teeth are kept usually very clean, yet when I view them in a magnifying mirror, I find growing between them a little white matter, as thick as wetted flour in this substance, though I could not perceive any motion, I judged there might probably be living creatures I therefore took some of this flour, and mixed it either with pure rain water wherein were no animals, or else with some of my spittle, having no animals nor air bubbles to cause a motion in it, and then to my great surprize perceived that the aforesaid matter contained very many small living animals, which moved themselves very strangely. The largest sort were not numerous, but their motion strong and nimble, darting themselves through the water or spittle, as a jack or pike does through the water The second sort spun about like a top, and were more in number than the first In the third sort I could not well distinguish the figure, for sometimes it seemed to be an oval, and other times a circle these were exceedingly small, and so swift, that I can compare them to nothing better than a swarm of flies or gnats, flying and turning among each other in a small space * * * * The number of these animals in the scurf of a man's teeth are so many, that I believe they exceed the number of men in a kingdom For on the examination of a small parcel of it, no thicker than a horse-hair, I found so many living animals in it, that I guess there might have been 1,000 in a quantity of matter no larger than the one-hundred part of a sand [grain]"

Of the many ingenious controls which Leeuwenhoek devised, bearing upon the question of origin and survival of protozoa and bacteria, no description can be given. With his infusions of pepper, ginger, and nutmegs; his search of waters from various sources and after various periods of storage; his comparisons of the living creatures in the deposits between the much washed teeth of ladies of his

acquaintance and from the neglected teeth of old toppers; his personal experiences with mouth washings with strong vinegar and hot coffee, he learned much of the life and possibility of survival of these minute forms. Thus he is justly placed by de Kruif as "the first of the *Microbe Hunters*"

SPERMATOOA

Many of the letters of Leeuwenhoek dealt with the male reproductive cells, which he observed in numerous species His first letter on this subject was dated November, 1677, and was published in the Philosophical Transactions for 1679. In this he makes it clear that he first saw spermatozoa at the suggestion of Johan Ham who had discovered them while a student at Arnheim Ham never published his observations Priority of description then rests with Leeuwenhoek At this time, also, he described for the first time the crystals of spermine phosphate Urged by the Secretary of The Royal Society to extend his observations, he sent on March 18, 1678, drawings of the animalcules which he observed in the seminal fluids of the dog and rabbit, and by 1683 Leeuwenhoek had examined the seminal animalcules in almost all classes of animals and had substituted the theory of generation *ex animalculo* for that of *ex ovo* Some believed that he had discovered the homunculus of Paracelsus but in a letter published in 1699 he stated emphatically that he had never seen the semblance of the human form in the structure of the spermatozoon Statements of various biographers to the contrary are due to a curious error Leeuwenhoek had accepted seriously a

certain communication which was falsely signed Dalenpatius, and repeated the imaginary cuts of the practical joker, who was its author, in commenting adversely upon it. These crude figures showed the spermatie homunculus in the act of bursting forth from its investing membrane. Due, in part, to an error in placing these figures, it was assumed that they represented Leeuwenhoek's opinion, whereas the contrary was the case. He did believe, however, that he had distinguished sexual differences between spermatozoa, and suggested that they might be able to reproduce themselves as do other minute animals, but if so, the small stage must be passed through very rapidly for they were found to be all of approximately the same size.

THE CIRCULATION OF THE BLOOD

Harvey had described and proved the existence of a circulation, Malpighi had discovered the capillaries, but Leeuwenhoek was the first to see the

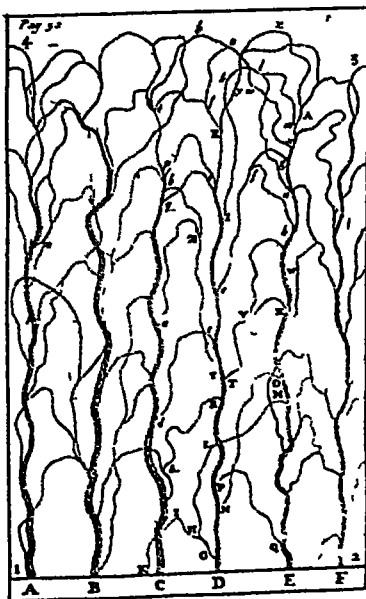


FIG 4 The capillary loops as seen by Leeuwenhoek

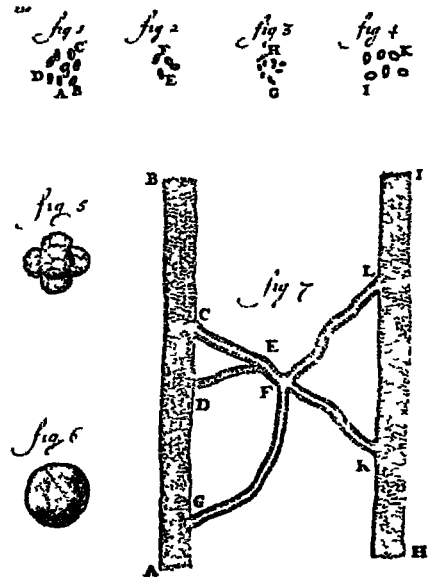


FIG 5 Above are blood corpuscles of various species, and in fig 7, the passage of the corpuscles from artery to vein through the capillaries

passage of the corpuscles of the blood from the arterial to the venous channels. His first success was with the tadpole. I quote from Hoole's translation of the letter in which Leeuwenhoek described this observation:

"Upon examining the tail of this creature, a sight presented itself, more delightful than any that my eyes had ever beheld, for here I discovered more than fifty circulations of the blood [figure 4], in different places, while the animal lay quiet in the water, and I could bring it before the microscope to my wish. For I saw, not only that the blood in many places was conveyed through exceedingly minute vessels, from the middle of the tail towards the edges but that each of these vessels had a curve, or turning, and carried the blood back towards the middle of the tail, in order to be again conveyed to the heart. Hereby it plainly appeared to me, that the blood-vessels I now saw in this animal, and which bear the names of arteries and veins are, in fact, one and the same: that is to say, that they are properly termed arteries so long as they convey the blood to the farthest extremities of its vessels, and veins when they bring it back to the heart [figure 5]."

What manner of man was this whose interests covered so wide a range and who found something new wherever he searched? By his works, his many letters and certain extant portraits we must judge him. Unlearned in the scholastic sense, but by no means illiterate, an obstinately persistent searcher who never knew defeat; intellectually honest in that he described faithfully that which he *saw*, and carefully differentiated from it that which he *thought*, stubborn, selfish, for he reserved certain lenses and certain methods for himself alone; sensitive, but at the same time self-satisfied in

the knowledge of the superiority of his knowledge, Leeuwenhoek was above all else an overwhelmingly accurate man. When, in 1723, and at the age of ninety-one years, Leeuwenhoek was on his deathbed, he called to him his friend, Johannes Hoogvliet, and asked him to translate two more letters into Latin and send them to The Royal Society. They were received posthumously. Thus Antony van Leeuwenhoek was for more than fifty years a searcher for truth. He had a profound respect for Authority, but for him Authority was vested only in Nature.

BIBLIOGRAPHY

- BECKING, L. B. Antoni van Leeuwenhoek, immortal dilettant (1632-1723), *Scientific Monthly*, 1924, xviii, 547-554.
- BEIJERINCK, M. W. Verzamelde Geschriften, vol v, (De infusies en de ontdekking der bacterien, 119-140), Delft, 1932.
- CAMAC, C. N. B. Imhotep to Harvey, 1931, Paul B. Hoeber, Inc., New York City.
- COLF, F. J. Early theories of sexual generation, 1930, Clarendon Press, Oxford.
- DE KRUIJ, PAUL. Microbe Hunters, 1926, Harcourt, Brace and Company, New York City.
- DE TONI, G. B. Nella ricorrenza del II centenario della morte di Antonio van Leeuwenhoek frammenti cestoniani inediti, *Arch di Storia della Scienza*, 1923, iv, 233-240.
- DONIL, CLIFFORD. A protozoological bicentenary Antony van Leeuwenhoek (1632-1723) and Louis Joblot (1645-1723), *Parasitology*, 1923, xv, 308-319.
- HAAKMAN, P. J. Antony van Leeuwenhoek, *Nederlandsch Tijdschr v Geneeskunde*, 1871, vii, 1-86.
- HARTING, P. Das Mikroskop Theorie, Gebrauch, Geschichte, und gegenwartiger Zustand desselben, 1859, 1866, Friedrich Vieweg und Sohn, Braunschweig.
- LEEUEWENHOEK, A. VAN. Brieven 4 vols, Leiden and Delft, various publishers.
- RICHARDSON, B. W. The asclepiad a book of original research and observation, 1885, Longmans, Green, and Company, London.
- STUBBS, S. G. B., and BLIGH, E. W. Sixty centuries of health and physics, 1931, Paul B. Hoeber, Inc., New York City.
- Antony van Leeuwenhoek 1632-1723, *The New England Jr of Med*, 1932, ccvi, 195-197.
- VAN LEEUEWENHOEK. The Philosophical Transactions of The Royal Society of London, Abridged, Vols II to VI.

Editorials

THE TERCENTENARY OF ANTONY VAN LEEUWENHOEK

On the twenty-fourth day of the month of this issue the scientific world celebrates the three hundredth anniversary of the birth of Antony van Leeuwenhoek. The phrase, "the scientific world," is used advisedly for there are few branches of science which do not owe much to the insatiable curiosity of this honest Dutchman. Particularly do the microscopists claim him for their own, the bacteriologists, protozoologists, and micro-phytologists, but the physiologists, chemists, and crystallographers likewise have a claim. A fuller appreciation than the editorial columns permit is published as the final article in this issue.

PRIMARY CARCINOMA OF THE LUNG IN THE MINERS OF JOACHIMSTAL

Editorial reference has been made in the ANNALS¹ to the accumulating evidence that radio-activity may be an important extrinsic factor in the etiology of cancer. Attention was called to the radio-activity of the ore in the oft-quoted Schneeberg mines, in which the miners have been known to suffer to a peculiar degree from pulmonary disease since this *Beigkrankheit* was described by Agricola in 1500. It is now well established that this illness

was very frequently primary carcinoma of the lung. Less has been known until recently in regard to the occurrence of a similar affection in Joachimstal, a mining town of about 8,000 inhabitants, situated on the Bohemian side of the Erz Mountains, in Czechoslovakia, about 30 kilometers southeast of Schneeberg. There is now available a delayed report of the investigations by Pirchan and Siki² in this village. Here the *a priori* assumption that a significant rôle is played by radio-active substances seems all the more justified for Joachimstal has been famous as a source of radium since the beginning of the present century. It was from pitchblende from this source that Mme. Curie isolated radium, and at the present time there is an annual production in the government factory of about two grams of radium chloride annually. The waters of the mines are strongly radio-active also. There had been knowledge of a considerable mortality from pulmonary disease among the miners of Joachimstal for a long time but proof of its cancerous nature was lacking. The first case of cancer of the lungs in a radium factory worker

¹EDITORIAL. Internal radiation in the causation of malignancy, ANN INT MED 1932 v, 932-934

²PIRCHAN, AUG, and SIKI, H. Cancer of the lung in the miners of Joachimstal (Joachimstal), Am Jr Cancer, 1932 vii 681-722

in this village was observed by Pirchan in 1926. During the period (1929-1930) covered by the investigation quoted, 19 miners died, of whom ten belonged to the active staff and nine were pensioners. Upon these it was possible to make postmortem examinations in but 13 cases. Nine proved to have cancer of the lungs.

As in the similar situation in the Schneeberg mines the etiological factor, the cancerogenic agent, has not been determined with certainty. These mines have in common the presence of arsenic compounds, some of which are volatile and are found in the air of the mines. Chemical analyses of human tissues have failed to show arsen-

ic, but this evidence is not conclusive. As to the content of radium emanation in the air of the three pits now being worked at Joachimstal, the conditions are very similar to those in the Schneeberg district. In various levels and at various times there is a great quantitative difference, ranging from 4 to 52 maché units, which corresponds closely with values up to 50 maché units as determined in the Schneeberg mines. Although yet unproved, radium emanation, exerting a cumulative effect when inspired for a period of years, must be considered the most probable extrinsic etiological factor in the primary carcinoma of the lungs in these miners.

Abstracts

The Chief Remarks to the First Graduating Class of the Medical Department of Duke University on the Occasion of the Planting of a Sprig of Ivy from 13, Northam Gardens. By WILLIAM S. THAYER, M.D. (New England Jr. Med., 1932, cccvii, 563-570.)

Not to abstract—for it would be little less than sacrilege for the abstractor to mar the unity of this delightfully informal address—but to call attention to its very existence and place of publication is the purpose of this reference. All of that great host who hold Osler in loving memory through close association with him and the still greater host of those inspired by his life and works will read and reread this brilliant appreciation, prickled with reminiscences, by one who can say: 'For to us who were close to him during the last thirty years of his life, he will always stand out a figure apart from most other men.'

Cysts of the Dysentery-Producing Endamoeba Histolytica in a Baltimore Dog. By JUSTIN ANDREWS. (Am. Jr. Trop. Med., 1932, xii, 401-404.)

A wire-haired fox terrier, born and reared near Baltimore, became ill when about six months old and passed gelatinous, stringy, mucus-containing stools which were occasionally diarrheic. In the simple smears from the stool, two types of amebic trophozoites were found, from the general appearance of which a tentative diagnosis of *Endamoeba histolytica* and *E. coli* was made. Subsequent examination of the stained smears showed in addition, both eight- and four-nucleated cysts, in all respects resembling the cysts of these two amebae respectively. The finding of cysts of *E. histolytica* in a naturally infected dog is apparently a unique observation. If the identification of the organism was correctly made, it means that this dog was a carrier and constituted

an available reservoir for pathogenic amebic infection in man and dogs

Lawrence-Moon-Biedl Syndrome By WILLIAM ANTHONY REILLY, A B, M D, and HANS LISSER, A B, M D, (Endocrinology, 1932, xvi, 338-357)

Two certain and two doubtful cases of the Lawrence-Moon-Biedl syndrome are reported, and are combined with 73 acceptable cases from the literature in a tabular analysis of this extremely interesting complex. The six cardinal symptoms—obesity, genital dystrophy, retinitis pigmentosa, mental deficiency, polydactylism, and familial occurrence—are by no means all invariably present. Such groupings as obesity, genital dystrophy, and retinitis pigmentosa, obesity, mental deficiency, and retinitis pigmentosa, and retinitis and polydactylism, are encountered. Unless the complete syndrome is present, familial occurrence is necessary for positive diagnosis. In the reported cases there are 25 with complete findings. Some authors have found symptomatic improvement on endocrine replacement therapy, using various combinations of thyroid with pituitary and ovarian extracts. The obesity and the mental retardation have been relieved to varying degrees by such management. Two of the cases reported in this paper have responded well to endocrine therapy. Loss of weight, increased animation, and definite improvement in vision have occurred.

Effect of Carbon Arc Irradiation on the Goiter-Producing Substance in Plants By BRUCE WEBSTER (Proc Soc Exp Biol and Med, 1932, xxix, 1070-1072)

Freshly harvested cabbage from a source which had previously been shown to produce active goitrogenic plants, was finely divided, spread out in thin layers, and irradiated with a carbon arc for 20 minutes at a distance of 50 cm. This cabbage was then fed to normal rabbits in quantities yielding 60 calories per kilo per day. Unirradiated cabbage from the same source was fed in equivalent amounts to a similar series of rabbits as a control. All rabbits used in the experiment were injected subcutaneously with 5 mgm of potassium iodide one week

prior to beginning the feeding experiment, to insure complete involution of their thyroid glands. When these animals were killed at the end of the experiment, it was found that the thyroids of those receiving irradiated hashed cabbage had an average weight of 554 mgm, while those of the same number of animals in the control series, which had received non-irradiated hashed cabbage, weighed 248 mgm when averaged. Thus it appears that carbon arc irradiation increases the goiter-producing power of cabbage, probably through a photochemical reaction leading to the formation of the goitrogenic substance.

Cultures of Leukemic Blood Leucocytes By MILA PIERCE, M D (Arch Path, 1932, xiv, 295-322)

By a modification of the Maximow method of tissue culture the white blood cells from a number of patients with leukemia were cultured. These cultures were observed in the living condition, also fixed at six hour intervals or less during the first 24 hours, and at 12 hour intervals or less after that time. After fixation in Zenker's solution plus formaldehyde, they were embedded in celloidin, serially sectioned and stained with a hematoxylin-eosin-azure II solution. Two patients with chronic myelogenous, one with chronic lymphatic, three with myeloblastic, and one with acute lymphatic, leukemia furnished the white blood cells upon the cultures of which detailed observations were made and reported in this paper. In the myeloid and myeloblastic types, myelocytes, polyblasts, fibroblast-like cells, monocytes and hemocytoblasts developed in the cultures. In the chronic lymphatic type, a few monocytes, many polyblasts and fibroblast-like cells appeared, although many of the explanted cells remained unchanged. In the acute lymphatic type, monocytes, polyblasts, fibroblast-like cells and epithelioid cells developed in large numbers, as well as hemocytoblasts morphologically identical with those found in lymphnodes and bone marrow. The unitarian view of the formation of blood cells—that is, that the hemocytoblast or large lymphocyte of the blood and lymphatic tissue is endowed with pluripotentiality as to development, is the theory which

gains the most support from this investigation

Duodenal Ulcer Following Skin Burns By JOHN H. FITZGIBBON, M.D. (Northwest Medicine, 1932, xxxi, 427-430)

Fitzgibbon reviews the literature of duodenal ulcer subsequent to cutaneous burns. This condition was first described by Dupuytren in 1832. Since then many examples have been reported but almost all have been fatal cases, discovered, or at least verified, at the autopsy table. The author's two cases both recovered. In the first, symptoms of duodenal ulcer appeared in the second week after receiving severe burns of the head, neck, and forearms. A few weeks later there was severe bleeding as shown by tarry stools. X-ray examination showed slight distortion of the duodenal cap, which has

since disappeared. The Sippy treatment was rigidly observed for over a year, and recovery has been complete. The second patient also was burned about the upper part of the body, but the diagnosis of ulcer was not made until about five and one-half months after the injury. There was then a distorted duodenal cap. Under medical management there has been progressive improvement. The author considers that this condition is much more common than has been supposed, and that ulceration with symptoms of moderate severity may be overlooked because of the absence of hemorrhage or perforation. The accumulation and study of cases of this group have significant importance in determining the medicolegal status of duodenal ulceration following burns.

Reviews

The Sign of Babinski: A Study of the Evolution of Cortical Dominance in Primates By JOHN F. FULTON, Sterling Professor of Physiology in the Yale University School of Medicine, and ALLEN D. KELLER, Professor of Physiology and Pharmacology in the School of Medicine, University of Alabama. 165 pages, 65 illustrations. Charles C. Thomas, Springfield, Ill., and Baltimore, Md. 1932. Price \$5.00 postpaid.

The preface explains the publication of a monograph on an "isolated neurological sign" and thus disarms criticism on that score. The book is divided into six chapters, an appendix and a bibliography. Babinski's original description of the reflex sign known by his name is followed in order by a study of the plantar reflex signs in the monkey, the baboon, the gibbon, and the chimpanzee under normal circumstances and in conditions of operative experimentation. Then is considered the evolution of cortical dominance while the appendix deals briefly with the general procedures of anesthesia, and a technique of electro-surgical methods

and surgical aftercare. The various experimental protocols are reported with faithful detail. There is ample evidence that the entire research was planned not only with an eye to the elucidation of the problem under immediate investigation but also with a mind open to seize upon such data as may be of value in solving a variety of related neurological problems. Each experiment is briefly summarized at the beginning of its protocol, which makes it possible to read with a greater appreciation. The illustrations are plentiful and serve their purpose well. Some may wish that the authors had allowed themselves a greater latitude in discussing the theoretical aspects of the problems involved, but, after all, the presentation and summarizing of objective data must be the *sine qua non*. Some of the experimental findings could as well have been related to the vexed clinical problem of the "diffuse sclerosis" as to the syndrome described by Little. This monograph should have a definite appeal to investigators in clinical and experimental neurology and to neuropathologists.

H. G.

Diseases of the Coronary Arteries (Myocarditis) By DON C. SURRON, M.S., M.D., Associate Professor of Medicine, Northwestern University, Attending Physician, Cook County Hospital, Chief, Cardiac Follow-up Clinic, Cook County Hospital, Chicago, and HAROLD LUETH, Ph.D., M.D., Formerly Instructor of Physiology, Northwestern University, Chicago. 164 pages, 42 illustrations, and 3 color plates. C. V. Mosby Company, St. Louis, 1932. Price, \$5.00.

In the first chapter of this work, entitled "Symptomatology", an excellent discussion is presented covering not only the symptoms of disease of the coronary arteries, but also the possible etiological factors in acute conditions and the mechanism of the production of symptoms in angina pectoris. Experimental evidences and clinical examples are given to emphasize the various points made. There is also a discussion of differential diagnosis. The latter part of the chapter deals with coronary thrombosis and myocardial infarction. These subjects are covered concisely, omitting little if anything of clinical importance concerning them. The second chapter discusses the physical findings in the arteriosclerotic heart including a moderately long discourse on the electrocardiograms of the various types of heart block. In chapter III a short resume of the anatomy of the heart with regard to its blood supply is given. Special emphasis is placed on the existence of anastomoses among the vessels of the heart which increase in number with age and thereby enable the myocardium to withstand certain vascular accidents. In chapter IV there is a discussion of the pathology of the coronary vessels and the resultant myocardial changes. The opinions of many authors are quoted concerning the nature of these changes, their etiology, etc. The fifth chapter deals with the physiology and pharmacology of the coronary arteries. The first part discusses in some detail the experimental procedure used in studying the flow of blood through these vessels and the effects of various physiologic processes including nervous control upon the rate of flow. The latter portion takes up the effect of certain drugs on the coronary blood flow as determined from ani-

mal experiments. The final chapter is devoted to therapy and gives in a clear, concise manner the latest information on the use of drugs, rest, diet, etc., in the treatment of disease of the coronary arteries. This work is well written throughout and should be of value to the medical student in his clinical years and to the practicing physician.
B. M. H.

Physiology of Bacteria By OTTO RAHN, Professor of Bacteriology, Cornell University, Ithaca, New York. 438 pages, 42 illustrations. P. Blakiston's Son and Co., Inc., 1012 Walnut St., Philadelphia, Pa., 1932. Price, \$6.00 net.

It is to be emphasized that *Physiology of Bacteria* by Rahn is not a text in bacteriology. It is above all a study in physiology. In the words of the preface, "It is an attempt to co-ordinate the various simplest functions of life, to study each function in itself and in its effects upon the other functions." The main topics considered are Endogenous Catabolism, Energy Supply of the Cell, Growth, and the Mechanism of Death. The method of development of the subject is logical, giving experimental evidence and applying mathematical analyses to the data obtained. As indicated, only the most fundamental life-phenomena are investigated, and so similar are such life-processes in all protoplasm that the results are in a measure applicable even to man. Well written and well printed, this book should interest the advanced students in both physiology and bacteriology. Careful reading of this book and appraisal of its mathematical analyses will prove a useful exercise for workers in biometric studies in general. To all of these groups it can be fully recommended.

The Expectant Mother's Handbook By FREDERICK C. IRVING, A.B., M.D., Professor of Obstetrics, Harvard Medical School, Visiting Obstetrician, Boston Lying-in Hospital. 203 pages, 26 illustrations. Houghton Mifflin Company, Boston and New York. The Riverside Press, Cambridge. 1932. Price, \$1.75.

While the average expectant mother finds the Government Bulletin adequate, this small book is, of course, much more con-

plete and should provide an answer for most of her questions. The subject matter is presented in a concise manner but nothing is slighted and the illustrations, too, are entirely suitable. There is one point that should be brought up to date, as Dr Irving has given the old-fashioned method of diaper folding! From the title of the book the chapter on evolution and heredity was a bit unexpected, but if the reader has no previous knowledge of biology she will learn much of interest to her, and will enjoy the clear exposition of Mendel's Law, even though it is too late to profit by this newly acquired knowledge. The expectant mother will find it altogether worth reading. One can forgive what seems to be a rather unnecessary beckoning of the attention toward the various toxemias of pregnancy including eclampsia—the mother's doctor should watch out for these—when the emphatically reassuring pronouncement denying all significance to maternal impressions and prenatal culture is reached in the final pages.

R C W

Behavior Aspects of Child Conduct By ESTHER LORING RICHARDS, B A, M D, D Sc, Associate Professor of Psychiatry, Johns Hopkins School of Medicine, Physician-in-Charge of Dispensary, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital. With a Foreword by ADOLF MEYER. 299 pages. The Macmillan Company, New York City, 1932. Price, \$2.50.

From a rich experience and unusual opportunities has developed this sensible book on the behavior problems of children and adolescents. It is characterized by sympathetic treatment and by the common sense simplicity of presentation. It is entirely free from the sonorous nomenclature which

constitutes the professional jargon of so much of the day's applied psychology. This book should be familiar to every pediatrician, neurologist, and general practitioner to whom parents come with problems of "badness" in children. Throughout, the medical aspects are given adequate weight. Numerous well chosen case histories add interest and promote understanding. Some passages approach the epigrammatic: "Better chickenpox and blasphemy than a child established in habits of selfishness inevitably associated with being solitary in all his ways" (See also quotation on page 541).

Die Klinik des Diabetes mellitus im Kindesalter [*Diabetes Mellitus in Childhood*] By Privatdozent Dr F. FREISE and Dr J. M. JAHR. (Reprinted from *Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten*, Heft 30.) 57 pages, several text figures and two folding tables. S. Karger, Karlstrasse 39, Berlin, Germany. 1932. Price in paper, M. 4.80.

As the title states this monograph treats of the clinical aspects of juvenile diabetes mellitus. About 20 pages are devoted to the metabolism of the diabetic, the significance of protein, fat and carbohydrate for the diabetic organism, and the action of insulin. Further sections deal with the practical application of these principles in diagnosis, with consideration of hereditary and constitutional etiological factors, and with management. Under the latter heading the procedures indicated in the presence of infection and in those cases seen in coma or in a state of hypoglycemia are described. Discussion of the results to be expected from treatment, the prognosis, and a short bibliography conclude the article.

College News Notes

Acknowledgement is made of the following gifts to the College Library of publications by members

- Dr H Sheridan Baketel (Fellow), Jersey City, N J—1 reprint,
Dr William C Boeck (Fellow), Los Angeles, Calif—1 reprint,
Dr Grafton Tyler Brown (Fellow), Washington, D C—1 reprint,
Dr Edward E Cornwall (Fellow), Brooklyn, N Y—3 reprints,
Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,
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Dr Norman Strauss (Associate), New York, N Y—2 reprints,
Dr Douglas Brown (Fellow), Castle Point, N Y—1 reprint,
Dr C Lydon Harrell (Fellow), Norfolk, Va—4 reprints,
Dr George H Hoxie (Fellow), Kansas City, Mo—1 reprint,
Dr S J McClendon (Associate), San Diego, Calif—5 reprints,
Dr Martin J Synnott (Fellow), Montclair, N J—1 reprint

A paper on "Treatment of Pneumonia in Childhood" was presented before the Bradford County Medical Society at Towanda, Pa, July 26, 1932, by Dr William F O'Donnell (Fellow), Clinical Professor of Pediatrics at Georgetown University, Washington, D C

Dr Sinclair Luton (Fellow), St Louis delivered a paper entitled "The Clinical Use of Digitalis", before the recent meeting of the Missouri State Medical Association

Dr Louis Faugeres Bishop (Fellow), and Dr Louis Faugeres Bishop, Jr (Fellow), New York City, had published in the June International Clinics a paper on "Subacute Bacterial Endocarditis", with a colored drawing as a frontispiece, and with other illustrations

On August 1, 1932, Dr Ralph deBallard Clarke, (Fellow), Meriden, Conn, under the auspices of the State Tuberculosis Commission of Connecticut was transferred from Undercliff Sanatorium at Meriden to a more diversified and enlarged field at Laurel Heights Sanatorium at Shelton, Conn

Dr R R Janjigian (Fellow), Wilkes-Barre, Pa, addressed the Luzerne County Medical Society, September 7, 1932, on "Transfusion Problems"

Dr C Ray Lounsberry (Fellow), San Diego, Calif, has been elected president of the staff of the Scripps Memorial Hospital

Dr Guy G Lunsford (Fellow), Millen, Ga, Commissioner of Health for Jenkins County, was recently appointed from the First District, by the Medical Association of Georgia, on a Committee to "Study the Cause of Maternal Deaths and Infant Mortality"

The Jenkins County Board of Health recently sent Dr Lunsford to Williamson County, Tenn, to observe tuberculosis control work being done there

Dr Frederic J Farnell (Fellow), Chairman of the Public Welfare Commission for the State of Rhode Island, is the author of an article entitled, "Development of Mental Health in Childhood", which appeared in the United States Daily, August 6, 1932

Dr Curran Pope (Associate), Louisville, Ky, read a paper on Personal Observa-

tion upon Pyretotherapy, or Fever Treatment" before the Louisville Society of Medicine during July. Dr. Pope also read a paper entitled, "Clinical Studies in Pyretotherapy, or Fever Treatment" before the summer meeting of the Muldraugh District Medical Society at Lebanon, Ky., August 11, 1932.

Dr. Burt R. Shurley (Fellow), Detroit, Mich., in recognition of his service in the American Expeditionary Forces at Base Hospital No. 36, has been cited to receive the "Order of the Purple Heart."

Dr. Russell Richardson (Fellow), Philadelphia, is a member of the staff in charge of clinic service of the George S. Cox Medical Institute for Research and Diabetes at the University of Pennsylvania Hospital. The Cox Institute was opened March 18, 1932.

Dr. Cyril N. H. Long, formerly Associate Professor of Medical Research, McGill University Faculty of Medicine, Montreal, has been appointed Director of the Institute

Dr. Harry L. Arnold (Fellow), Honolulu, Hawaii, contributed the chapters on the "Physiology of Respiration", "Pathological Physiology of the Thorax", "The Role of X-ray in Thoracic Surgery", and "Therapeutic Pneumothorax", in "Surgery of the Chest" by Dr. George F. Straub.

Dr. Collins H. Johnston (Fellow) of Grand Rapids, Michigan, delivered an address on the Life of Robert Koch, to 300 nurses of Grand Rapids recently.

Dr. William H. Gordon (Fellow), Detroit, Michigan, addressed the Hancock County Medical Society at Hancock, Michigan on September 7, 1932, speaking on the topic, "Agranulocytosis".

Dr. J. A. Myers (Fellow), Minneapolis, Minn., addressed the joint meeting of the Mississippi Valley Conference on Tuberculosis and Mississippi Valley Sanatorium Association, September 12 to 14, 1932, held at Indianapolis, Ind., on "Tuberculosis Infection—Relationship of Tuberculous Child-

hood Infection to the Adult Type of Tuberculosis" and "Tuberculosis As a 'Teen Age Problem: The Challenge of High School Teachers and Teacher Training Schools'".

Dr. Arnold S. Anderson (Associate), St. Paul, Minn., also addressed the above meeting on "Tuberculosis Among Nurses".

Dr. Myers also spoke before the Eleventh Annual Meeting of the West Virginia Tuberculosis and Health Association, September 6-7, 1932, held at Elkins, W. Va., on "Tracing Tuberculosis to Its Source".

Dr. William H. Walsh (Fellow), Chicago, Ill., presented two papers at the Thirty-Fourth Annual Convention of the American Hospital Association in Detroit, September 12 to 16, on "The Relation of the Source of Capital Investment Funds to the Cost of Hospitalization" and "Hospital Planning and Construction—Preliminary Procedures to Assure Economy and Efficiency". These will be published in the 1932 Transactions of the American Hospital Association.

Dr. Salvatore Lojacono (Fellow), Marquette, Mich., was elected President of the Michigan Sanatorium Association at its recent meeting held during August, 1932.

Dr. Leon T. LeWald (Fellow), New York, N. Y., read a paper on "Congenital Absence of Superior Orbital Wall Associated with Pulsating Exophthalmos, Report of Four Cases (Lantern and Motion Picture Demonstration)", before the meeting of the American Roentgen Ray Society in Detroit, September 29, 1932.

Dr. Albert S. Hyman (Fellow), New York, N. Y., addressed the American Congress of Physical Therapy on September 7, 1932, at the meeting held in New York City, his subject being, "Electrocardiographic Control of Diathermic Therapy in Coronary Thrombosis and Angina Pectoris". The paper was discussed by Dr. A. E. Parsonnet (Fellow), Newark, N. J., and Dr. Louis F. Bishop (Fellow), New York, N. Y.

Dr. Hyman was also recently elected Secretary of the Harlem Medical Association of New York, one of the oldest medical societies of the country.

OBITUARIES

DR EDWIN MASSIE BELL

It is with deep regret that announcement is made of the death from bronchopneumonia, of Doctor Edwin Massie Bell, which occurred Saturday, August 20, at George F Geisinger Memorial Hospital, Danville, Pennsylvania

Doctor Bell was born at Lenoir, North Carolina, October 27, 1897, the son of Edwin L. and Elizabeth Massie Bell. His early education was obtained at the Greenbrier Military Academy, Lewisburg, West Virginia. He received his bachelor's degree from Washington and Lee University, Lexington, Virginia, and graduated from the Medical School of the University of Pennsylvania, in 1922. He served in several hospitals in Philadelphia during the next several years and later became Chief Resident at the Episcopal Hospital in Philadelphia. In 1925, tuberculosis developed and he came to Devitt's Camp at Allenwood, Pennsylvania. After a period of rest and recuperation, Doctor Bell was appointed an Associate Physician on the Staff of Devitt's Camp.

Doctor Bell was an ideal physician, having not only a marvelous insight and understanding of medicine, but also of the minds and hearts of his patients and people generally. He possessed the rare faculty of immediately creating a feeling of confidence and security in the minds of his patients, and in their personal problems of life was a sympathetic and helpful counsellor. He possessed rare qualities of friendship and it was said of him that he never gave up a friend. His brilliant

personality, cheerfulness, and lovable qualities endeared him to his associates on the Staff and to hundreds of patients and friends. His philosophy was that no situation in life was impossible, and his ability to create a rational outlook on life in the minds of his patients suffering with tuberculosis was one of his most marvelous accomplishments. Although Doctor Bell's life was comparatively short, it is certain that he accomplished in a few years what it oftentimes takes other men a lifetime.

Dr Bell was a member of the American Medical Association, of the National Tuberculosis Association, and an Associate in the American College of Physicians.

(Furnished by WILLIAM DEVITT, M D, F A C P, Allenwood, Pennsylvania)

DR CHARLES JOSEPH DURAND

Dr Charles Joseph Durand (Fellow), Colfax California died, suddenly, July 6, 1932, following an operation for hernia, aged forty-five years.

Dr Durand was born in Coaticook, Province of Quebec. His preliminary education was obtained at St Hyacinthe's Seminary, St Hyacinthe, Quebec. He graduated from the Medical Department of Laval University, Quebec, in 1911. Shortly after graduation he moved to California because of tuberculosis. For eighteen years he was associated with the Colfax school for the Tuberculous at Colfax California, having served as Assistant

Medical Director for the past fifteen years

Dr Durand was a Past President of the Placer County Medical Society, Past President of the California Northern District Medical Society, a member of the California Academy of Medicine, a member of the California Medical Association, a Fellow of the American Medical Association and a member of the National Tuberculosis Association

At the time of his death he was Medical Health Officer for Colfax, Examining Physician for many years for the Placer Union High School at Auburn, California, and Associate Secretary-Treasurer of the Placer County Medical Society. He had been a Fellow of the American College of Physicians since 1931

(Furnished by ROBERT A PEERS, M D, C M, F A C P, Colfax, California)

The November Issue of the Annals of Internal Medicine

Fungus Infections of the Central Nervous System	WALTER FREEMAN
Errors in the Diagnosis of Jaundice Observations Based on 533 Cases Verified by Operation or Necropsy	GEORGE B EUSTERMAN
Early and Late Effects on Peptic Ulcer of Parenteral Injections of a Non-specific Protein	
Also Conclusions Drawn from Experimental Work on the Modus Operandi of the Therapeutic Agent and the Etiology of the Lesion Helped by It	LAY MARTIN
The Clinical Diagnosis of Pulmonary Arteriosclerosis	HENRY L. ULRICH
A Summary of Recent Studies on Equine Encephalomyelitis	K F MEYER
Sensitization to Fungi	GRAFTON TYLER BROWN
Ten Years at the Lymanhurst School for Tuberculous Children	J. ARTHUR MYERS
Friction Rub over the Liver in a Case of Subacute Bacterial Endocarditis	MILOSH KASICH
The Migraine Syndrome	OLIVER T OSBORNE
The Trend in Cerebral Localization	LEWELLYS F BARKER

Fungus Infections of the Central Nervous System

By WALTER FREEMAN, M D , P H D , F A C P , *Washington, D C*

INVASION of the central nervous system by the higher fungi is a comparatively rare condition, but a number of such cases have been reported during the past few years, especially in America, and it is my privilege to present the results of a comparative study of some twenty-five cases. I take the immediate opportunity of thanking those who have contributed to my collection of pathologic material.

The first cases adequately studied were reported in Germany by von Hansemann and by Turk in 1905 and 1907, although the condition probably was recognized by Zenker in 1861. Curtis, in 1895 and 1896, reported from the Institut Pasteur the case of a young man who developed myxomatous tumors in the groin and lumbar region due to yeast infection and who later succumbed with meningitic symptoms, but necropsy was not performed, so that some doubt must be entertained concerning the invasion of the central nervous system by the fungi. The cases of von Hansemann and of Turk, however, shortly followed by that of Benda, established infection of the central ner-

vous system by fungi upon a firm basis. Only in Turk's case was the diagnosis made during life, although the yeast cells were undoubtedly seen in the sediment of the spinal fluid of all three cases. In Benda's case they were not taken seriously, and in that of von Hansemann the patient was so far advanced in pulmonary tuberculosis that the diagnosis of tuberculous meningitis was made. Cultures were obtained in the cases of Turk and Benda. Turk gives an amusing account of his astonishment upon finding yeasts in the spinal fluid.

Da jetzt jede Verunreinigung vollkommen ausgeschlossen war, musste ich zu der Überzeugung kommen, dass tatsächlich Hefe im Rückenmarkskanale der Kranken vorhanden sei, und dass sie dann eine Bedeutung für die Pathogenese der Erkrankung habe, erschien mir eigentlich selbstverständlich. Ich bat damals sogleich auch den Pathologen unseres Spitals, Professor Kretz, sich einen "verrückten" mikroskopischen Befund, von dessen Herkunft ich ihm gar nichts verriet, anzusehen. Kretz meinte zunächst, ich wolle ihn "aufsitzen" lassen und habe ihm einen drabetischen Harn mit Hefeansiedlung eingestellt. Als ich ihm dann von der Abstammung des Präparates Mitteilung machte, stimmte er meiner Auffassung, dass eine Hefemaision der Meningen vorliegen müsse, vollkommen bei.*

Presented before the First International Neurological Congress, Berne, Switzerland, September 3, 1931. From St. Elizabeth's Hospital, Washington, D. C. Received for publication, December 15, 1931.

*Now that contamination was fully ruled out, I had to conclude that actual yeasts were present in the patient's spinal fluid and that they were of pathogenic importance in the disease seemed axiomatic. I

In all these cases the involvement of the central nervous system was outstanding and few or no other lesions referable to fungi were found in other parts of the body. Shortly after these reports in the German literature, however, there occurred in Chicago a remarkable series of generalized infections by a different type of yeast-like organism, LeCount being the first to describe in detail the lesions in the central nervous system. Infection of the skin by *Blastomyces* (*Oidiomyces*) had long been recognized. However, in a number of foreign laborers who lived in a mouldy cellar, the superficial lesions were followed by spread of the infection through the body, involving the lungs, bones and internal organs, and sometimes the brain. The skin, however, was always involved and usually presented the primary lesion. Wade and Bell collected the cases in a comprehensive report.

The prominence accorded this type of infection led to confusion, and blastomycosis was only later separated into its different entities comprising torulosis, saccharomycosis and oidiomycosis, chiefly by Stoddard and Cutler. Nearly at the same period, 1909, Evans described involvement of the nervous system by another of the higher fungi, *Coccidioides immitis*, the organism being quite different from those previously described, although the histo-

then asked Professor Kretz, the pathologist of our hospital to examine a "crazy" microscopic finding, without giving him its source. Kretz thought I was "kidding" him and was showing him a diabetic urine inoculated with yeast. But when I told him of the origin of the preparation he agreed entirely that there must be a yeast invasion of the central nervous system.

pathology was in many respects similar. More recently, two other fungi have been reported as invading the central nervous system, namely *Endomyces capsulatus* and a sporothrix. I have studied material from 19 cases of torulosis, and one each of coccidioidial granuloma, oidiomycosis, endomycosis, sporotrichosis, and aspergillosis.

CLINICAL FEATURES

The symptomatology of fungus infection of the nervous system varies to some extent, depending upon the manner of involvement. In some cases the general symptoms of headache, vomiting and stupor betray the general involvement of the meninges and intracranial hypertension, while in others the focal symptoms are predominant. In those cases in which the invasion of the nervous system is secondary to involvement elsewhere, there is usually a focus to be found in the skin, bones or respiratory tract, but in practically all cases in which the nervous system is involved, the predominant clinical features are those connected with the nervous system.

There is usually some record of disturbance in health before the onset of the cerebral symptoms. Certain patients are, as Turk puts it, "zumeist kranklich," suffering from respiratory or digestive symptoms, although indications of cerebral disorder are less common, and mental symptoms are rare. Cutaneous lesions are infrequent in torulosis but are common in coccidioidial granuloma and especially in oidiomycosis. The disease sometimes sets in violently with severe headache, vomiting and vertigo but more often insidiously with pain over the sinuses

or behind the eyes, intermittent at first but later becoming continuous. Stiffness of the neck and neuralgic pains in the limbs and back are commonly mentioned. Staggering and ataxia are seen, with disturbances of sleep, and in some cases faults of memory and irritability that may lead to a clinical diagnosis of organic dementia. Vomiting occurs in

of four in torulosis. Anorexia and vomiting produce an emaciation and debility that may reach an extreme degree. The circulation and respiration are affected only in the latest stages. Moreover the laboratory findings are not characteristic if one excepts the spinal fluid examination. Leucocytosis is mild in most cases, eosinophilia ab-



FIG. 1. Oidiomycosis. Intermediate power view of the lesion in Gaspár's case showing abscesses and giant cells, with a high power view of the organisms.

many cases, without disturbances of the bowels. Failing vision is usually a late phenomenon, diplopia is fairly common, though deafness is less frequent. Hemiplegia is rare in torulosis but is found especially in oidiomycosis. Paraplegia was reported in one or two cases of torulosis but is apparently more common in coccidioidal granuloma.

The general symptoms of acute infectious disease are commonly absent. Fever occurs in cases of generalized oidiomycosis, but only in one case out

of four in torulosis. Anorexia and vomiting produce an emaciation and debility that may reach an extreme degree. The pressure of the spinal fluid is often increased, and the cell count may be numbered in hundreds. On the other hand, the pressure may be normal and the cells little increased. In a few instances there is a complete block. Among these cells, yeast-like bodies are apt to be found, sometimes in large numbers. If the organisms are recognized by the alert pathologist the diagnosis is immediately made. Too often,

however, it would seem that the cells are examined under low power or after drying and staining, and are not recognized as fungi. The body cells in the fluid are mostly lymphocytes, although an admixture of polymorphonuclear leucocytes to 30 per cent may be found. Cultures are usually positive. Serologic investigations have revealed no agglutination, precipitation or complement fixation in either human or animal infections. Chemical studies are negative. Animal inoculation may reproduce the cerebral disease.

A number of patients have been subjected to operation upon the suspicion that a tumor might be present. In certain instances the surgeon has recognized the granulomatous character of the process at operation, or the pathologist has reported the finding of the characteristic lesions or organisms in the biopsy specimen. The later course of the disease is almost progressively downward, death resulting in from two to six months. This may be delayed in some instances by repeated lumbar punctures, and only one instance of sudden death following puncture is reported. Provided no intercurrent infection supervenes, the patient usually sinks into coma and dies of respiratory failure.

The clinical picture, then, is usually one of chronic meningitis or cerebral tumor, occasionally suggesting organic dementia of senile or luetic type, but at other times dominated by focal symptoms and signs.

Many varieties of treatment have been attempted, but the mortality in torulosis and in coccidioidal granuloma has been 100 per cent. One case of *oidiomycosis* with meningeal signs re-

covered, and Klarfeld has reported the finding of healed lesions in the experimental cerebral disease. Iodides and lumbar puncture have probably kept patients alive for a period. The extraordinary resistance of *Torula* to aniline dyes makes their use impracticable.

PATHOLOGY

Torula produces a great diversity of pathologic lesions in the central nervous system, while the lesions produced by other varieties of organisms are more or less uniform from case to case. It would appear from comparative mycologic studies now being carried on by Weidman that there are several species of torulae that may invade the nervous system, whereas the causative organisms concerned in the other cases, such as *oidiomycosis* and coccidioidal granuloma, show less variation.

Torula. Three special types of lesions occur in *Torula* infection, meningeal, perivascular and embolic. In nearly half the cases the meninges alone are invaded, although in most cases a few of the organisms will be found in the perivascular spaces close to the surface. The meningitis in such cases is usually nodular and may be mistaken grossly for tuberculous infection. The nodules are described as pale, grayish and translucent, adherent in some cases but easily lifted off in most. Histologically there is a pronounced reaction on the part of the meninges with localized fibrosis, endothelial hyperplasia and giant cell formation, occasionally associated with caseation. Organisms are found in considerable abundance, particularly if a silver impregnation is used. There may or may not be adhesion to the underlying cor-

tex In the cerebellum, however, there is often a granulomatous meningitis that causes marked adhesion of the neighboring leaflets. Inflammatory manifestations in the meninges are fairly marked, with numbers of lymphocytes and occasional plasma cells, but polymorphonuclear leucocytes are never found.

In the other half of the cases there are striking intracerebral lesions. Most of these would appear to be embolic since they are found in the gray matter of the basal ganglia and in the subependymal structures of the midbrain as well as in the cortex. All would appear to originate about the small vessels. Intravascular organisms are seldom found and no occluding clumps. The lesion begins with widening of the perivascular space and multiplication of the endothelial cells. The limiting wall of fibrous tissue is first stretched and then broken, bringing the organisms

into direct contact with the cerebral parenchyma. The reaction to this insult varies from case to case. In some there is tremendous hyperplasia of the endothelial elements with the formation of granulomas containing giant cells and lymphocytes but no leucocytes. The boundaries are usually sharp, but no wall of connective tissue separates the mass from the surrounding parenchyma. In others the lesions become cystic, being ballooned out into more or less rounded structures filled with gelatinous material that does not flow out when the cyst is cut across. Moreover, the cysts are usually multilocular, and when well developed give to the cortex the appearance of soap-suds. There is extraordinarily little reaction about the walls of the cysts in such cases, merely a few endothelial cells swollen to huge proportions by their enclosed organisms, and a feeble reaction on the part of the fibrous tissue of the vascular

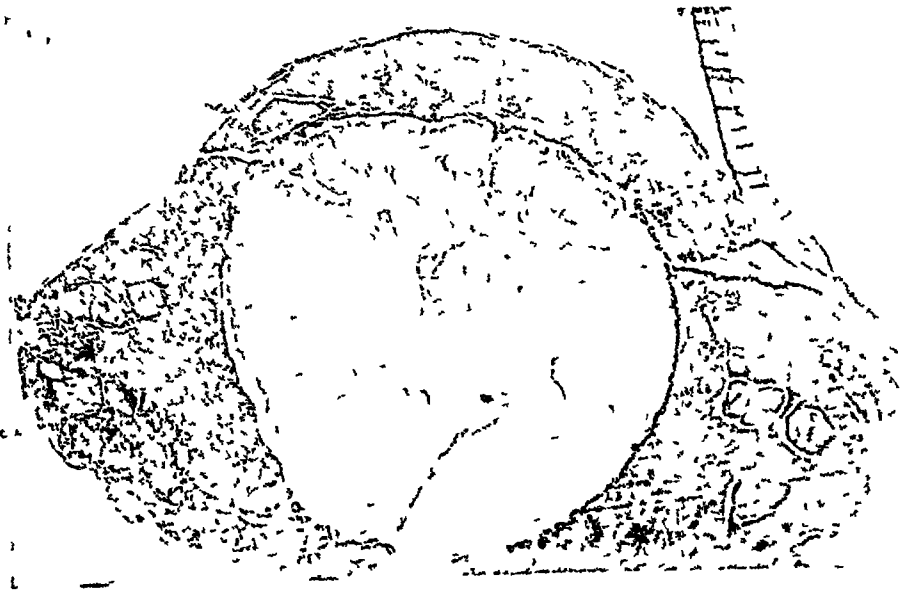


FIG. 2 Coccidioidal granuloma. Low power view of the lesion in Rinds second case. The spinal meninges are thickened by a massive granuloma surrounding the cord and compressing the nerve roots.

wall Small vessels with a delicate reticulum of fibrous tissue may be found in the middle of these cysts The interior is filled with organisms and fluid in variable proportions but never with necrotic débris Sometimes these are true yeast tumors, while at other times there seems to have been blocking of the fluid pathways along the vessel with the accumulation of large quantities of fluid and relatively few organisms The trabeculae are made up principally of compressed cerebral parenchyma, and nerve fibres can be demonstrated, as well as a few glia fibrils, but usually no connective tissue In the immediate vicinity of the cysts may be seen compressed nerve cells, considerably distorted, but retaining their staining qualities to a remarkable extent The cysts are evidently formed by the growth of the organisms with resulting compression of the neighboring parenchyma, a fact that was recognized originally by von Hanseemann

The reaction on the part of the neuroglia is usually slight or nil, but in one case in which widespread invasion of the tissue had taken place, astrocytes were beautifully demonstrated by Dr Cone, and were present in some profusion (Figure 6) In this same case there was rather marked increase in the number of rod cells in the cortex In most cases, however, there is surprisingly little general reaction to the invasion Fat and iron are practically absent

The embolic lesions in the depths of the brain may reach rather large proportions and are sometimes abundant These present much the same picture as do the superficial lesions, but the trabeculae are apt to be much larger and

often contain numerous connective tissue fibres Moreover there is apt to be slightly more lymphocytic reaction in the vicinity Caseation is not encountered, and there is compression rather than destruction of the neural parenchyma These masses often bulge into the ventricular lumen, and sometimes rupture with scattering of the contained organisms

In a few locations in most of the cases studied there would appear to be invasion of the perivascular space from the exterior although the possibility must be admitted that all the intracerebral lesions originated as embolic foci In one case with very rapid course and sudden termination, large flask-shaped cysts were found communicating with the subarachnoid space by small openings and it would seem that the organisms had gained entrance to the cortex by way of the perivascular ostia and by their growing mass produced the large cavities Moreover, in the brainstem and about the hippocampal region there were found in many cases small areas of perivascular invasion directly beneath the pia, communicating by small openings with the subarachnoid space Since there were no embolic lesions in the cerebral cortex, it would seem that there had been invasion of the perivascular space from without

Invasion of the nerve roots is rather frequent, and the gasserian ganglia have shown lesions in some instances Only once or twice has invasion of the spinal cord been demonstrated

The other organs of the body are affected in more than half the cases Lesions of the lungs preponderate Sometimes the foci in the lungs call attention to the previously unrecog-

nized cerebral invasion, while at other times the existence of well defined ulcerative tuberculosis conceals the lesions of torulosis. Acute miliary torulosis of the lungs has been reported. The lymph nodes are invaded in some cases, giving the picture of a typical Hodgkin's disease. Ulcerative lesions of the intestine with nodules on the peritoneum have been found in certain cases, the organisms being demonstrated in them. In a few cases there has been generalized infection with foci in the bone marrow, spleen, adrenals, liver and elsewhere, and a positive blood culture during life. Exudates in the pharynx have occurred a few times, and in one case a true ulcerative lesion of the skin occurred, torulae being demonstrated by smear.

On the basis of morphology, the organisms concerned have been grouped

in three types, with fairly good clinical and pathological correlations. The organism is rounded to oval, sometimes convexo-concave, having a mucinous capsule and one or more fatty dots in the interior. It reproduces in the tissues by budding. The size varies from 2 microns to 40. The smallest organism has been separated as a special type since it occurred in a case with rapidly fatal termination and had provoked large flask-shaped perivascular cysts with practically no reaction. The largest organism has been found in a number of cases in which the disease was limited to the meninges and in which the reaction of the mesoblastic elements was the greatest. The intermediate organism, ranging from 5 to 10 microns in diameter, is particularly liable to form intracortical cysts and granulomas as well as to invade the other or-



FIG. 3 Coccidioidal granuloma, Intermediate magnification showing the type of tissue in the granuloma. The giant cells contain organisms.

gans of the body. Cultural studies are useful in differentiating *Torula* from other genera but have not yet differentiated the various species of *Torula*.

Oidiomyces. The effect of invasion of the central nervous system by *Oidiomyces* (*Blastomyces*) is usually quite different from that produced by *Torula*. Only in one or two instances has generalized meningitis resulted, while the meningeal invasion is always present in torulosis. Instead, there are formed lesions considerably resembling tubercles or gummas, usually multiple and sometimes of large size. LeCount reported a mass half as large as the cerebellar hemisphere, and in Gáspár's case a large tumor-like lesion was situated over the surface of the cortex.

Infection of the brain by *Oidiomyces* is apparently always secondary to infection of the skin or lungs, although the primary focus may be hidden. This is in contrast to the condition prevailing in torulosis, where the cerebral infection is apparently primary in most instances. The reports of primary blastomycotic or oidiomycetic meningitis in the literature are probably to be interpreted as torulosis. The Chicago cases were all associated with foci in the skin, bones and lungs. The typical history of such a case was the development of a primary cold abscess of the skin with progressive suppuration and ulceration, later the development of other cutaneous and subcutaneous nodules and painful swellings in various parts. The invasion of the bones gave rise to localized destruction, sometimes with pathological fracture, and the involvement of the lungs, to a picture of chronic tuberculosis. Cerebral symptoms were apparently not observed, al-

though in one or two cases, headache and vomiting gave rise to the suspicion of meningitis. The spinal fluid yielded no specific information. In Gáspár's case a lesion of the brain was found at operation but necropsy was not performed. There were no cutaneous lesions.

Diffuse oidiomycetic meningitis occurred in one of the Chicago cases, but in the others there were multiple nodules resembling tubercles and situated in various locations. In the case reported by Gáspár there was a large grayish mass adherent to the dura and to the underlying convolutions. This was removed surgically but the patient died several weeks later. In contrast to tuberculosis, a blastomycotic tubercle is very firm and rubbery, and has a trabeculated appearance on section with small areas of necrosis.

Microscopically, the essential lesion is a miliary abscess that tends to heal with the production of large amounts of fibrous tissue and a central zone of necrosis. This process is repeated over and over again, and in the central portions the fibrous tissue breaks down into caseous material with more or less obliteration of outline. Giant cells are fairly abundant, belonging to the foreign-body type, and they contain organisms. Organisms are found also in the miliary abscesses and embedded in the fibrous connective tissue. Infiltration by lymphocytes and plasma cells is quite marked and endothelial cells are abundant. In the older fibrous and necrotic portions of the mass, leucocytes are no longer found, but they are abundant at the margins. There is a tendency toward building up and breaking down of a limiting wall against the in-

vasion process. When the lesion is meningeal there is direct involvement of the cortex, a condition that occurs but seldom in *Toxula* infection.

The organism is rounded, measures from 5 to 10 microns, has little or no capsule, and reproduces in the tissues by budding. It responds best to silver impregnations but can also be brought out by aniline dyes. In ordinary preparations it is unstained but highly refractile and often appears to have a double contour, probably indicating a narrow capsule.

Coccidioides. Coccidioidal granuloma bears a considerable resemblance to oidiomycosis in that the primary lesion is usually cutaneous although certain instances are on record where the meningeal invasion appeared to be primary. The lungs, bones and internal organs often suffer. The invasion appears most often to follow involvement of the vertebrae. In Ryfkogel's case the

cutaneous lesions were followed by a basilar meningitis that provoked hydrocephalus. In the two cases reported by Rand there were focal lesions compressing the spinal cord, one appearing as a dull red firm mass of extradural tissue resembling sarcoma, and the other a grayish sheath investing the upper part of the spinal cord and lower medulla. In the first case the lesion was successfully removed, the patient recovered from the paraplegia and was well some eight months later. The second patient died without operation. Both had evidences of spinal subarachnoid block, and were suspected of having tumors.

The pathologic process is a well-knit granuloma with abundant fibrous tissue and a tendency to the formation of nests of infiltrating cells. Most of these are lymphocytes and fibroblasts, but endothelial cells, plasma cells and leucocytes are occasionally found. Giant cells are numerous, large in size, with

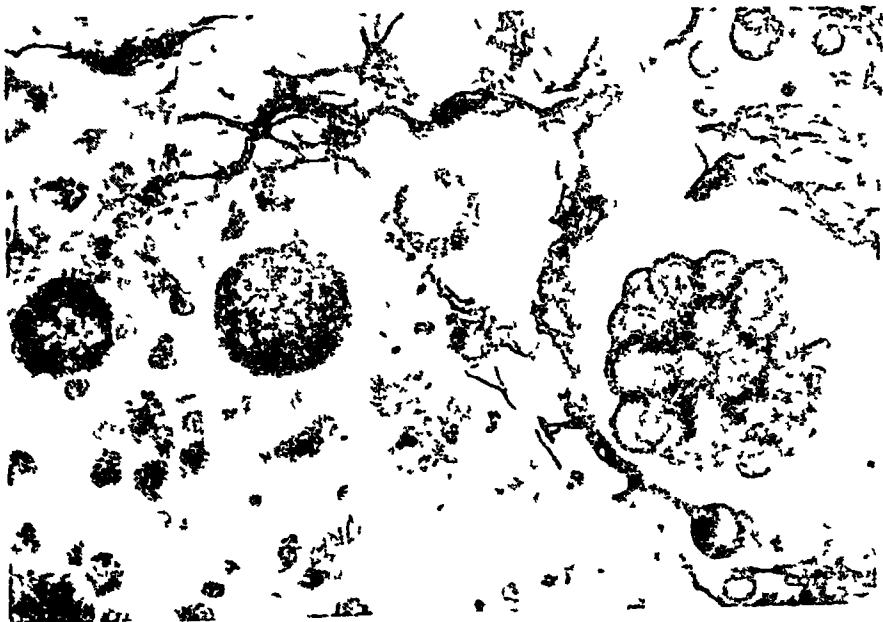


FIG. 4. Coccidioidal granuloma. High magnification showing the process of sporulation in the organism, Perdrau, $\times 650$.

many nuclei, rather irregular after the manner of foreign body giant cells. Necrosis is very slight. The most characteristic feature of the process is the presence of the offending organisms in moderate numbers. These are unmistakable even in ordinary preparations. They range from 10 to 100 microns in diameter, the larger ones showing sporulation, so that one membrane may contain from ten to fifty new organisms. Budding is not seen. Some of them have a double contour, but no mucinous envelope. The smaller ones are often found in endothelial cells and particularly in giant cells. The process in Rand's second case, which I have been privileged to examine, surrounded and compressed the nerve roots but did not penetrate the limiting membrane or involve the neural parenchyma. There was, however, abundant evidence of venous stasis in the cord, with a little perivascular infiltration probably due to degeneration.

Endomyces Only one case of this condition has been reported, but I have seen the sections through the courtesy of Dr. F. B. Mallory. This occurred in a furrier and lasted nearly six months. It began with granulomatous masses in the neck and thigh, headache and disorientation, and was complicated by pulmonary tuberculosis, a positive Wassermann reaction and 5 per cent eosinophilia. The picture of chronic meningitis persisted throughout. At necropsy there were found firm flesh-colored nodules widely distributed in the cerebral meninges. None were found in the interior of the brain.

Histologically, the lesions were circumscribed but not encapsulated, and consisted of very cellular fibrous tissue

permeated with endothelial cells and foreign body giant cells. Lymphocytes and plasma cells were less abundant. Certain areas were necrotic and infiltrated with leucocytes. The organisms were found in the endothelial and giant cells. They were very small, averaging 1.6 microns in diameter, although larger forms were sometimes found. They possessed a small unstained capsule and one to three nucleoids per cell, and they reproduced in the tissue by budding. The mycologic characters of the organism placed it in a new species. It proved pathogenic for animals. The masses in the neck and thigh were of the same causation.

Saccharomyces It is uncertain whether a case of meningeal saccharomycosis has been reported. The case of Curtis was not followed by necropsy, and the organism in Turk's case was probably a torula. Badham reported from Australia a case in which the organism resembled the one described by Curtis, but the pathologic report is too sketchy to be of value, merely indicating that a granulomatous type of meningitis was present.

Sporothrix The only case of sporothrix meningitis is that reported by Hyslop *et al.*, although Dominguez described a case of extradural abscess complicating sporothrix infection of the middle ear. The condition was recognized by finding the spores and mycelia in the spinal fluid, but cultures and animal inoculations were negative. The illness lasted six months with exacerbations and remissions, tetanoid attacks, microptic hallucinations and uncinatiform fits. No infection of the skin or mucous membranes was discovered even at necropsy and the internal or-

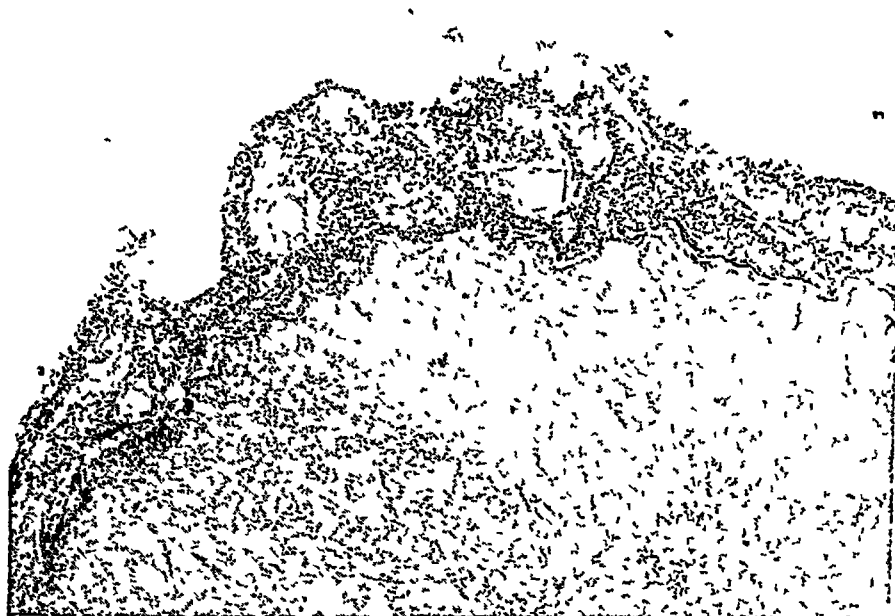


FIG 5 Sporotrichosis Low power view of the spinal cord in the case of Hyslop *et al*, showing the moderate meningeal infiltration and fibrosis without necrosis or giant cell formation

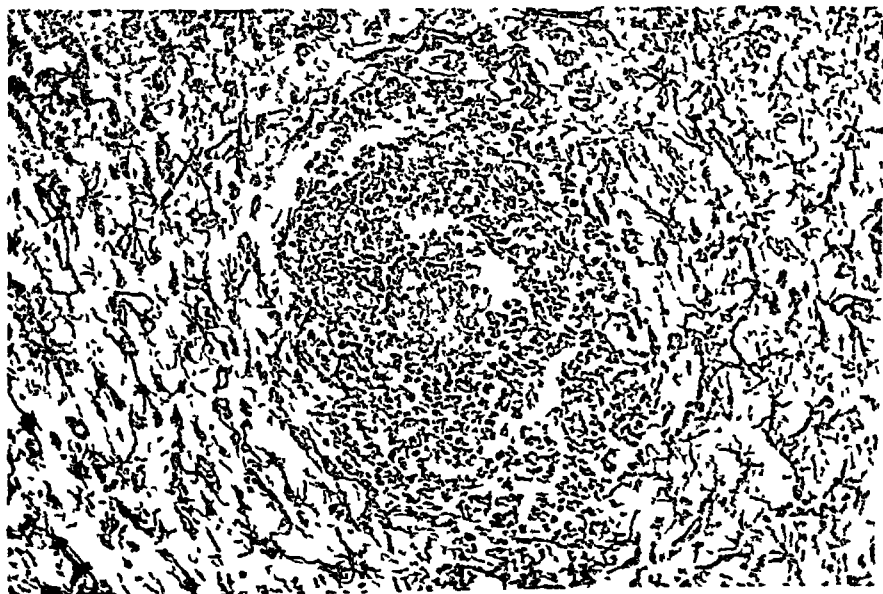


FIG 6 Torulosis Intermediate power view of one of the focal embolic lesions of the cerebral cortex showing the hypertrophied astrocytes Preparation of Dr William Cone of Montreal

gans showed no involvement. The base of the brain showed a marked accumulation of cloudy fluid, and between the cerebellar hemisphere was a gelatinous mass, with marked thickening of the arachnoid. A similar condition was observed along the course of the left optic nerve. The condition was limited to the membranes. There was some increase in fibrous tissue with marked infiltration by lymphocytes, plasma cells and endothelial cells. This was particularly pronounced over the cerebellum, the temporal lobe, and the upper end of the spinal cord. Organisms were very difficult to find in the sections and silver impregnation did not demonstrate them. There was, however, a marked discrepancy between the degree of fibrosis observed in the ordinary preparations and that seen by the Perdrau method, so that the fibrillar material observed in the former may have contained some closely packed mycelia.

Aspergillus. Infection of the eye or ear by *aspergillus* is no great rarity, but very few cases of cerebral involvement have been reported. In the case reported recently by Egas Moniz and Loff, a white woman, aged 44, developed iridocyclitis with some inflammation of the vitreous, the cause of which was not determined. After a period of three years in which pain in the eye was the dominant symptom, blindness supervened. There was no headache, but the patient became confused and delirious. The definitive onset was with slowly progressive spastic hemiplegia that terminated in death within three weeks. There was only a terminal rise in fever, mild anemia and no leucocytosis. The spinal fluid pressure was normal, the albumin moderately increased,

the cell count 72 per c mm. Necropsy disclosed no lesions outside of the brain and eye. The meninges were thin. There was a destructive lesion suggestive of a granuloma in the left frontal lobe affecting the internal capsule and the head of the caudate nucleus. The central portion showed marked necrosis, about the periphery were milium abscesses that tended to heal with the production of considerable amounts of fibrous tissue infiltrated with lymphocytes, plasma cells and endothelial elements. Giant cells were numerous, large, and contained many fungi. The fungi were filamentous, branching, rather tortuous and of deep brown color, easily recognized in unstained specimens. Some of them lay free in the exudate of the small abscesses at the periphery. Other cases have been reported, according to the authors, by Ponfick, Arcé, Balado and Franke, Keller, and Orlow. Lacking cultural studies, the identity of the fungus is not certain since it might have belonged to the genus *Penicillium*.

SUMMARY

Invasion of the central nervous system by the higher fungi is characterized clinically by symptoms of chronic meningeal inflammation, sometimes associated with focal signs. Recognizable lesions of similar nature are often absent from other parts of the body, but the finding of the parasites in the spinal fluid establishes the diagnosis. From the pathologic standpoint the lesions are characterized by the formation of granulomata in the meninges and by varied lesions in the brain and cord. *Oidiomyces*, *Aspergillus*, and

Coccidioides provoke miliary abscess formation with tendency to heal, while *Torula* incites very little reaction and sometimes builds yeast tumors and cysts. The common portal of entry is probably the respiratory tract.

BIBLIOGRAPHY

Author's note Bibliography concerning fungus infections of the nervous system, as well as photomicrographs of the histopathology of torulosis will be found in the author's monograph "Torula Infection of the Central Nervous System" in the *J f Neurol u Psychol* 1931, xliii, 231-345

Recent articles are listed below

CHIARI, H Zur Pathologie und Histologie der generalisierten Torulose (Blastomykose), *Arch f Derm u Syph*, 1930, clxii, 422-441

DEMME, H, and MUMME, C Blastomykose des Zentralnervensystems *Deut Ztschr f Nervenheilk*, 1932, cxxvii, 1-26

EGAS, MONIZ, and LOFF, R Aspergillose cérébrale, *Press med*, 1931, xxxix, 273

GENEVAY and BABLET Sur un cas de blastomycose meningee a *Saccharomyces tumefaciens* à Tonkin, *Arch Inst Pasteur d'Indochine*, 1930, April, 33-44

REALE, E Un caso di meningite da torula histolitica, *Morgagni*, 1931, lxxiii, 66-68

URBACH, E, and ZACH, F Generalisierte Torulose (europäische Blastomykose) Eine klinisch-botanische Studie, *Arch f Derm u Syph*, 1930, clxii, 401-422

WATTS J W Torula infection, review and report of two cases, *Am Jr Path*, 1932, viii, 167-192

Errors in the Diagnosis of Diseases Associated with Jaundice

Observations Based on 533 Cases Verified by Operation or Necropsy

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IN this article I have, except occasionally, purposely excluded from consideration cases of icterus neonatorum, or congenital defects of the biliary tract, cases of jaundice the result of obvious hepatotoxins such as arsphenamine, chloroform and arsenic, or of industrial poisons, and cases of septic poisoning, infectious disease, cardiovascular disease, syphilis, decompensated portal cirrhosis, epidemic (catarrhal) jaundice, obvious primary hypertrophic biliary cirrhosis (Hanot), pancreatic cysts, carotinemia and advanced metastatic carcinoma of the liver. The material selected represents a fairly consecutive series of cases which are, to a large extent, representative of the type in which surgical measures for the relief of the jaundice were actually carried out or contemplated.

As in previous contributions, the following factors essential to a diagnosis were stressed: (1) The presence or absence of pain and its character, (2) information as to the patency of the bile passages, especially as shown by a study of the duodenal content, and of

the feces, (3) the van den Bergh reaction in the blood serum, and (4) the determinations of level and variability of the curve of serum pigment. To these may be added the evidence occasionally gained by the cholecystogram, especially in cases of low-grade jaundice not of too long duration, by "scout" films of the gallbladder and bile ducts, and by study of the bacterial and especially the microscopic elements of bile from the gallbladder and extra-hepatic bile ducts.

McNee's simple and practicable classification of jaundice, comprising four groups, obstructive, toxic, infectious and hemolytic, deserves attention. Rich, who has contributed to knowledge of the pathogenesis of the various forms of jaundice, is critical of McNee's classification. He points out that although the first and last divisions of this classification are based on pathogenesis, the second division is based on etiology. Although acknowledging the propriety of Rich's criticism, I question whether he has markedly lessened our diagnostic handicaps by his classification, for in the two main types of jaundice which frequently give rise to difficulty in differential diagnosis, namely, moderate to high-grade jaundice due to disease of the liver itself,

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and the more or less painless obstructive jaundice, his laboratory criteria are the same. Moreover, he includes both types in one division, classified as regurgitant jaundice, yet the former is nonsurgical and the latter invariably surgical, and frequently urgently so if irreparable injury to the hepatic parenchyma and vascular structures, and to the biliary tree and pancreas, or even a fatal issue, is to be avoided.

Jaundice is usually a dramatic clinical phenomenon, and although in many instances the causative factor is obvious, too often difficulties attending correct diagnosis are almost insurmountable. Increasing experience adds to a physician's humility, for it makes him cognizant of the various possibilities which may give rise to this condition.

Factors giving rise to difficulty in the expeditious appraisal of many cases of jaundice are as follows: (1) The absence of any trustworthy specific test consistently to distinguish between hepatic and obstructive jaundice (the need for such a test is frequently manifest when the obstruction is incomplete and has developed without painful accompaniment), (2) the association of several lesions, in the biliary tract of the same subject, one of which may give rise to jaundice *per se*, such as stones or calcareous material, or marked biliary cirrhosis, incident to a traumatic stricture of the common bile duct, multiple pigment stones in the gallbladder or common bile duct of the patient with hemolytic icterus, or the occasional association of stone in the common bile duct with carcinoma of the head of the pancreas, (3) pathologic conditions with which it is un-

usual to associate jaundice, and which on occasion may be severe and of long duration, such as calculous cholecystitis, the calculi being confined to the gallbladder, and (4) conditions difficult to recognize clinically and which may produce mechanical jaundice, such as chronic pancreatitis, obliterative cholangitis, benign and malignant tumors of the common bile duct, and especially inflammatory or suppurative lesions of the pancreas.

STONE IN THE COMMON BILE DUCT

Stone in the common bile duct has been the commonest cause of jaundice in my experience and was encountered in 147 of 533 cases. In most cases the stones were multiple, occasionally there were stones in the hepatic ducts. Not infrequently the surgeon noted a single stone confined to the common bile duct or ampulla, or even multiple stones in both. Cholecystic disease is from three to four times as common among women as among men. When the disease does occur in man he is five years older on an average than a woman with the same condition. Conversely, primary carcinoma of the pancreas or ducts is more common among men. In this group of cases of stone in the common duct the sex incidence was about equal, the number was too small for statistical purposes. One-fourth of these patients had submitted to a previous operation, usually drainage or removal of the gallbladder. In cases in which drainage was done a complete external biliary fistula was frequently present. This is invariably indicative of obstruction of the common bile duct, as shown by Balfour and Ross.

In 85 per cent of the entire group a correct primary diagnosis was made of the condition, and an alternative diagnosis in an additional 9 per cent, or in a total of 94 per cent. The chief cause for making an incorrect primary diagnosis (9 per cent) was probably due to the fact that the icterus was mild and transient, or both. Jordan and Weir have shown that almost 6 per cent of the patients with stone in the common bile duct may have no pain at any time, and 13 per cent may never be jaundiced. This incidence might have been even higher if a larger series of cases had been studied. The combination of severe recurring colic, characteristic in most cases, followed by definite icterus, frequently clinical and laboratory evidence of suppurative cholangitis, plus an average moderately elevated and fluctuating level of serum bilirubin explained by the fact that in 91 per cent of such cases the common bile duct is partially patent, is the outstanding clinical manifestation, and is striking enough to account for the high degree of diagnostic accuracy reported in this series. The average value for serum bilirubin was 9.1 mg for each 100 cc of blood. In a similar group studied by Weir, more than 70 per cent of the patients had values of serum bilirubin of less than 10 mg. In a survey of 1,608 surgically verified cases of choledocholithiasis Judd and Marshall observed that if a history is painstakingly obtained and the patient kept in hospital for a period of observation, surprisingly few errors in diagnosis will be made. Bockus and his associates claimed that 86.6 per cent of these cases exhibit evidence of calculus due to the presence of cholesterol crystals and calcium bili-

rubinate pigment in the bile obtained on duodenal drainage. Undoubtedly this diagnostic procedure should be more often resorted to in doubtful cases.

CHOLECYSTITIS WITH STONES

In a series of eighty-five patients with gallstones, who were jaundiced at the time they came under observation, the average serum bilirubin content of the blood was 7 mg for each 100 cc. In 67 per cent a correct primary diagnosis was made, whereas in 30 per cent of the remainder the jaundice was attributed to stones in the common bile duct. From a clinical standpoint this is one of the most interesting groups and seems to be proof of the observations made repeatedly for years by pathologists and surgeons in The Mayo Clinic concerning the association of the liver, pancreas and the extrahepatic biliary ducts in disease of the gallbladder. In sixty-five (77 per cent) of these cases there was gross evidence, at operation, of changes in the organs mentioned. Besides stones in the ducts, compression of the common bile duct from enlarged contiguous glands, and from abscess pockets with marked regional inflammatory reaction consequent to the perforation of stones through the gallbladder, was also noted. Frequently considerable dilatation of the common bile duct was recorded, as though a calculus which had previously obstructed the duct had recently been passed and this conclusion was strengthened by the fact that the patient had experienced colic just prior to operation, followed by icterus, which promptly and progressively began to subside.

Observations made by Hartman in 1,022 cases in which operation was

done in 1922 for cholecystic disease (associated with gallstones in 652 cases) demonstrated that 166 (27 per cent) of the patients, with gallstones and without evidence of choledocholithiasis or other obvious mechanical obstruction of the extrahepatic biliary ducts, gave a history of jaundice of variable degree and duration. Moreover, of 375 patients of this series, who had only chronic cholecystitis at operation, sixty (16 per cent) were having or had had jaundice, 26 per cent of these, as discovered by the surgeon, had pancreatitis also. It is not of so much practical import that the jaundice was erroneously attributed to stone in the choledochus, as it is to remind the surgeon of a history of, or the presence of icterus so that the extrahepatic ducts of the liver and the pancreas will be adequately examined during the operation.

CARCINOMA OF THE PANCREAS

It is usually very difficult to make an unequivocal clinical diagnosis of carcinoma of the pancreas in the absence of jaundice. In a review of 138 cases of this entity in 1922, proved at operation or at necropsy, more than half of the patients, when first seen at the clinic, were without jaundice. In the presence of jaundice the combination of later adult life (average age fifty-six years), recent onset of subjective disturbances and objective signs, infrequency of actual painful seizures or colic, marked and progressive deterioration of weight and strength, high-grade bilirubinemia, with a high, rising, or fairly sustained pigment curve, when associated with palpable gallbladder and repeated absence of bile on duodenal drainage, makes the diagno-

sis fairly easy. Prior to operation, the correct primary diagnosis of carcinoma of the pancreas was made in 84 per cent of sixty-nine cases, and an alternative diagnosis was made in an additional 8 per cent, a total of 92 per cent. In a little more than 30 per cent of cases the duct is partially patent, and in the absence of pain and a palpable gallbladder the condition may be confused with the purely intrahepatic forms of jaundice, or silent stone in the duct. The clinical picture of carcinoma of the pancreas is indistinguishable from carcinomatous tumors of the common bile duct or papilla of Vater, especially in the absence of ulceration, infection and bleeding of the latter.

Complete obstructive jaundice may be caused by stones in the common bile and hepatic ducts, by stricture, by external compression or actual invasion of the common bile duct from carcinoma of the head of the pancreas, by primary carcinoma of the ducts, or by extension of a carcinomatous process from the gallbladder, stomach or duodenum. The pain of obstructive jaundice is chiefly dependent on the rapidity and degree of the obstructing agent. As a consequence there may be instances of stone in the common bile duct without pain, and pancreatic obstruction of the common bile duct with severe biliary colic. The last feature and the coexistence of gallstones in 12 per cent of cases, was responsible for the erroneous primary diagnosis of stone in the common bile duct in 14 per cent of the cases of carcinoma of the pancreas. Intrahepatic jaundice did not figure in the primary diagnosis, which attests to the trustworthy clinical features of the majority of cases of car-

cinoma of the pancreas, but the converse is not true, as will be observed. Of diagnostic and prognostic import, too, are Judd and Counseller's observations on the difference in the effect of benign lesions (stone, stricture) and carcinomatous obstructive lesions on the parenchymatous and vascular structures of the liver as well as on the intrahepatic and extrahepatic bile ducts.

To what extent the quantitative estimation of enzyme activity of the duodenal content is of diagnostic value remains to be seen. In the occasional cases without icterus but with associated occlusion of the pancreatic ducts, the gross characteristics and high fat content of the feces may furnish the first clue to the underlying pathologic change. Of added clinical interest is the occasional roentgenoscopic evidence of involvement of the stomach and duodenum, and rarely of the jejunum. The nature of these observations may be misinterpreted, especially in the absence of jaundice and in the event of obstruction of one of these organs which may occur. One outstanding characteristic of carcinoma of the pancreas is the persistence of jaundice, in contrast to stone in the common bile duct. In only two of many cases of jaundice with carcinoma of the pancreas was the jaundice known to clear entirely. This was the result of secondary ulceration, with temporary opening of the common bile duct and relief of the mechanical obstruction. The highest levels of serum bilirubin are seen in obstructive jaundice due to this lesion and in intrahepatic jaundice. In 75 per cent of a group of cases of obstructive jaundice studied by Weir, there was bilirubinemia of 11 mg, or

more. The average content of serum bilirubin in this series was 17.4 mg.

The following case illustrates exceptions to all rules that might be advanced in differential diagnosis.

A man, aged 72 years, first came to the clinic, February 25, 1932, with the complaint of pruritis of two and a half months' duration. For two or three years he had had some gaseous abdominal distress and bloating. Beginning one year before, he had experienced intermittent discomfort in the right upper quadrant of the abdomen, until three months prior to his admission. About this time, after he had returned from a trip to the mountains, he felt as though his bowels were clogged and took Epsom salts, a chill followed. The next day he had intermittent colic-like pains of moderate severity in the right upper quadrant, lasting for two hours. Two such attacks occurred within the next few days. A physician was not called, but heat was applied locally (hot water bottles) and the pain was relieved. The stools became putty-like, the urine dark, and itching and jaundice followed. During the following month there was no pain, the itching and jaundice gradually disappeared and the stools and urine resumed a normal color. After a brief respite, the icterus, pruritis, biliuria and acholic stools reappeared, but there was no pain. The pruritis was the most disturbing symptom and was present night and day. A week prior to his admission pain had returned for a brief period. The jaundice appeared to be lessening.

Moderate icterus of the sclerae and skin was noted on examination. The patient was comfortable except for the pruritis. There had been moderate loss of weight and strength and the edge of the liver was just palpable. Abdominal masses or tumors were not palpable, and there was no tenderness or rigidity in the right hypochondrium. During a period of observation in hospital the pruritis persisted, it was somewhat relieved by gynergen (ergotamine tartrate) administered orally thrice daily. Duodenal drainage always produced a free flow of clear amber bile, which contained a small amount of calcium bilirubinate pigment, but no cholesterol.

crystals or other abnormality The feces contained bile, but no occult blood The serum bilirubin fluctuated from an initial value of 58 to 21 mg for each 100 cc of blood Coagulation time (Lee) was somewhat prolonged There was moderate secondary anemia The urine was free from sugar on repeated examination, but following the intravenous administration of glucose, in preparation for operation, glycosuria and hyperglycemia were evident A galactose tolerance test was negative The concentration of urea rose from 44 to 62 mg for each 100 cc of blood The carbon dioxide combining power of the blood plasma ranged from 46.6 to 53.2 per cent by volume "Scout" films of the region of the gallbladder plainly showed the silhouette of a distended gallbladder, apparently filled with bile From time to time the patient experienced considerable pain in the right upper part of the abdomen, but never acute enough to justify the use of an opiate

March 17, laparotomy revealed a carcinomatous tumor of the head of the pancreas One week later the patient succumbed to hemorrhage and bronchopneumonia Necropsy revealed that the carcinoma partially compressed the lumen of the common bile duct

A history of pain was not obtainable at the outset, perhaps on account of the age of the patient and his fatigued, toxic state The condition on this account was regarded as an intrahepatic form of jaundice, because of temporary resolution of the icterus, its long duration, the patency of the duct, as determined by duodenal drainage, the low level of serum bilirubin, the absence of palpable gallbladder, negligible microscopic examination of the bile and negative galactose tolerance test (2.4 gm of sugar in the urine, normal more than 2.5 gm) The latter test may be negative during convalescence from infectious or long continued jaundice On the other hand, the recent onset of jaundice in an elderly patient,

its persistence, evidence of disturbed carbohydrate metabolism following the administration of glucose, suggesting injury to the pancreas by the factor that caused the jaundice, and the eventual admission of recollection of attacks of pain favored surgical exploration for what appeared to be obstructive jaundice from either stones or a new growth

In contrast to this patient was one in a nearby bed, a man fifteen years younger, with marked, more or less painless, jaundice of five weeks' duration, but without pruritis, an average level of serum bilirubin of 17.5 mg and a definitely enlarged, movable, insensitive gallbladder In addition, duodenal drainage for bile was repeatedly unsuccessful All of the evidence in the latter case was characteristic of carcinoma of the pancreas, a condition which was confirmed at operation

A palpable, distended gallbladder is of great diagnostic significance, and it is probably present in most cases of obstinate jaundice due to carcinoma of the head of the pancreas Recently it has been found advantageous to administer intravenously from 3 to 5 grains of pentobarbital sodium (sodium ethyl 1-methylbutyl barbiturate) if there are no direct contraindications Prompt and complete relaxation of the abdomen is thus secured, which greatly facilitates examination of a resistant abdomen In this manner it is possible repeatedly to palpate a distended gallbladder, as well as the pancreatic neoplasm, itself This drug is preferable to sodium amytal (sodium isoamyl ethyl barbiturate) as the patient recovers more promptly from the effect of the anesthesia

STRICTURE OF THE EXTRAHEPATIC BILE DUCTS

Benign stricture of the common or hepatic bile ducts, or both, as a cause of jaundice, does not loom large in medical literature, but the surgeon of wide experience is familiar with it, and it represents one of the most difficult of all problems in abdominal surgery. My series comprised sixty-seven cases, in which a primary correct diagnosis of the lesion was made in 63 per cent. In an additional 15 per cent, or a total of 78 per cent, an alternative preoperative diagnosis was recorded of stricture of the duct. The chief incorrect primary diagnosis (28 per cent) was that of stones in the common bile duct. This was to a certain extent unavoidable as in 24 per cent of the cases there were stones or stony material in the common bile duct or gallbladder, or both. The average level of serum bilirubin was 11.23 mg and occupied a position between that in cases of stone in the common bile duct and in carcinoma of the pancreas. This midway position is also true relative to the patency of the ducts, as in about 80 per cent the stricture was partially patent. In all but four cases operation had been performed for removal of the gallbladder. In one case cholecystostomy and drainage of an abscess had been done. In the three cases in which operation was not performed, the stricture was obviously due to obliterative cholangitis. In a careful review of preoperative and postoperative data, the impression was gained that the stricture was directly the result of surgical trauma to the duct. Judd has, on several occasions, described the conditions under which

trauma is sustained and how it may reasonably be avoided. Too often trustworthy clinical or laboratory evidence of pre-existing cholecystic disease was conspicuous by its absence, and this would vitiate the contention that the cholangitis present before cholecystectomy had persisted and progressed, and was the eventual cause of the stricture. As a consequence this complication should be suspected if evidence of extrahepatic obstruction of bile ducts follows removal of the gallbladder, especially if these phenomena are painless in onset and were not present before operation was undertaken. Many of the symptoms and eventual complications of traumatic stricture are common to stone in the duct, such as colic, pruritus, jaundice, chills, fever, and external biliary fistula, but the circumstances attending the inauguration of these symptoms is of direct diagnostic import. Variation in symptoms is due to the injury sustained, the nature and degree of repair when attempted and to the rate and degree of eventual obstruction and hepatic injury. In addition, bile stasis which is the result of stricture tends to cholangitis and the formation of stones or stony concretions. The latter sometimes obtain in the presence of rubber tubing used for anastomosis. In an attempt to differentiate stone in the common bile duct and stricture of the duct, certain clinical features are of relative importance. In case of stricture, symptoms invariably develop sooner after operation. In case of stone in the duct symptoms disappear on an average of three years and eight months after operation. The same is true of jaundice. There is a lower incidence of colic in cases of

stricture (about 30 per cent) in the absence of coexistent stone, whereas in the presence of stone, colic occurs in as high as 80 per cent. There is a higher incidence of pruritus in cases of stricture. Immediate postoperative jaundice, or persisting external biliary fistula, is suggestive of stricture. As a rule the flow of bile is scantier than in cases of stone in the duct and low fixed curves are invariably the result of biliary cirrhosis. Periods of increased bilirubin in the serum are concomitant with episodes of intermittent obstruction. It must be remembered that colic or jaundice, or both, following cholecystectomy, may supervene because of a stone in the duct which was overlooked even in the absence of calculi elsewhere, and stones have formed at varying intervals years after removal of a cholecystic gallbladder without stones.

CONGENITAL AND ACQUIRED HEMOLYTIC ICTERUS

The combination of clinical and laboratory data makes possible an accurate preoperative diagnosis in all of these cases. This series consists of thirty-eight patients, 58 per cent of whom were females. One-third of the patients were aged less than ten years. Thirty-four per cent had chronic cholecystic disease, eleven of the thirteen having calculous cholecystitis. With few exceptions the van den Bergh reaction remained indirect. The average level of serum bilirubin was 4.5 mg. in each 100 c.c. In several cases the initial test showed normal fragility which somewhat confused the issue temporarily, but which on subsequent examinations revealed the characteristic increased

fragility of the erythrocytes to hypotonic salt solution. The combination of low-grade icterus, secondary anemia, microcytosis, enlargement of the spleen, the youth of the patient in many instances, invariable indirect reaction even in the presence of gallstones, and the increased fragility of the erythrocytes, is characteristic of the disease, and makes possible an unequivocal diagnosis. There were no cases in this series of the characteristic pigment stone in the common bile duct, to produce associated obstructive jaundice. The results following splenectomy were universally excellent, and all but two of the patients survived the operation.

INTRAHEPATIC JAUNDICE

This generic term is applied to cases of diverse etiology in which the jaundice is the result of a disease process confined to the liver itself, in contrast to jaundice arising from mechanical obstruction of the extrahepatic bile ducts, from whatever cause. The series consists of thirty-five cases, in which twenty-six patients were submitted to operation. It is comprised chiefly of twenty-five cases of portal and biliary cirrhosis, hepatitis and subacute yellow atrophy, the latter followed cinchophen hypersensitivity or toxemia. In five of the cases gallstones were also present, in three cases the stones did not produce symptoms. A correct primary diagnosis was made in 54 per cent of the cases, and an alternative diagnosis in 14 per cent or a total of 68 per cent. The disease was chiefly confused with stones in the common bile duct (26 per cent) and carcinoma of the pancreas (17 per cent).

As previously stated, the highest readings for bilirubin are seen in cases of malignant obstruction and intrahepatic jaundice. In both instances the onset and course of the disease may be painless. This also applies to a small percentage of cases of stone in the common bile duct. Persistent absence of bile on duodenal drainage favors complete obstruction from carcinoma of the pancreas, impacted stone in the duct, or other mechanical factor, yet in the early stages of acute infectious or toxic hepatitis, or in certain stages of acute, severe types of hepatic jaundice, there may be temporary suppression of biliary excretion, or possibly obstruction to larger ducts by plugs of mucus, with similar negative results from duodenal drainage.

If patients are young the painless jaundice is invariably the result of infection or hepatotoxins, such as cinchophen, arsphenamine, oxyiodide and arsenic, and bacterial toxins of certain tropical diseases. If patients are elderly the diagnosis of catarrhal jaundice in the absence of endemic jaundice or obvious hepatotoxin, is usually erroneous. McVicar and Fitts felt that the cases of painless jaundice and a high degree of serum bilirubinemia offered the greatest difficulty in diagnosis. Weir, on the other hand, pointed out the great obstacles to successful distinction between hepatic forms of jaundice and obstructive jaundice if the obstruction is partial, and he stressed the need for some specific test especially if the obstruction has developed without the accompaniment of pain. To this end the galactose tolerance test has been employed whenever indicated and estimations made of the value of cho-

lesterol in the blood and cholesterol esters in an attempt to distinguish between obstructive and intrahepatic jaundice. The diagnostic value of the galactose tolerance and cholesterol tests will be appraised in the near future. As regards the former it promises to be of considerable value in the clinical differentiation of the painless or intrahepatic and obstructive forms of jaundice. In the first type in which as a rule the parenchyma is definitely injured, the galactose tolerance test is usually positive. However, in cases of long duration and in infectious jaundice during the convalescent period, the galactose tests may give negative results. Not infrequently positive results may obtain in obstructive jaundice, especially in cases of pancreatic carcinoma. At present one gets the impression that a positive result always signifies hepatic injury, but the injury may not necessarily be primarily hepatic. A negative test does not necessarily exclude an intrahepatic form of jaundice.

The practical aspects of the problem are obvious. One should not temporize in the presence of obstructive jaundice from whatever cause, if the surgical risk is not too great. Neither should one subject the patient to unnecessary, often hazardous operation if the evidence favors the nonobstructive form. The element of time under close observation in hospital is often a prime factor in successful differential diagnosis.

PRIMARY NEOPLASMS OF THE EXTRAHEPATIC BILE DUCTS

In this series were twenty-five cases, in all but two of which carcinoma was present. There were two benign tu-

mors, one a neurofibroma and the other an adenomatous cyst, both involving the common bile duct. In this series also there was a preponderance of males (68 per cent) and the average level of serum bilirubin was 16 mg. With the occasional exception of an ulcerating tumor of the papilla of Vater, or of the ampulla projecting into the duodenal lumen, this condition is indistinguishable from carcinoma of the pancreas if lesions are low in the duct, the condition may also perfectly simulate stone in the duct. Because of this fact and the comparative rarity of the lesion under consideration, in no instance was a primary correct diagnosis made, but an alternative or secondary diagnosis of carcinoma of the common bile duct was recorded in 20 per cent. An erroneous primary diagnosis of carcinoma of the pancreas was made in 52 per cent, of stone in the common bile duct in 44 per cent, and of stricture of the common bile duct in 4 per cent.

Marshall reviewed the cases in the clinic observed during a period of twenty years, ending January 1, 1930. There were forty-nine primary carcinomas of the common bile ducts, and four benign tumors. Three-fourths of the patients were aged more than fifty years, the male sex predominating. In 53 per cent of the cases disease of the biliary tract was associated, and in 43 per cent of these there were stones in the gallbladder or common bile ducts. This coincidence would partly account for the frequent diagnosis of stone in the common bile duct. The most common site of the new growth was in the lower end of the common bile duct or ampulla. The tendency to remission or intermittency of jaundice is more pre-

valent in cases of carcinoma of the common bile duct than in cases of carcinoma of the pancreas, but in a little less than half of the total number of cases cited by Marshall, the jaundice was extreme, constant and progressive. There may be complete absence of pain in a third of the cases. The lesions are small as a rule, metastasis is uncommon and late, technical surgical difficulties may be as insurmountable as the diagnostic difficulties, and widespread symptoms, with severe inflammatory and septic sequelae in ducts, liver or portal vein, are present sooner or later.

CARCINOMA OF THE GALLBLADDER

There were seventeen patients in this series, females predominating. The average age was similar to that in the series of neoplasms of extrahepatic bile ducts, and all were advanced in the fifth decade of life. The average value of serum bilirubin was 15.7 mg, the jaundice being due largely to extension of the process into the ducts and liver, or there was compression of the ducts by involvement of the lymphatic nodes at the hilum, or of nodes along the common bile duct. As there are no characteristic symptoms or signs of this neoplasm, a primary correct diagnosis, especially in the early, favorable stage, is rarely made prior to operation. The one exception in this series was a case in which exploration had recently been performed elsewhere. A primary erroneous diagnosis of cholelithiasis or choledocholithiasis was recorded in 59 per cent, and of carcinoma of the pancreas in 35 per cent. The invariable presence of stones in the gallbladder, cholecystitis or cholesterosis, often makes logical the diagnosis of stone in

the common bile duct, as noted, when jaundice supervened, whereas extension of the process into other organs, representing an advanced condition, with corresponding deterioration in general health, would make logical the primary erroneous diagnosis of carcinoma of the pancreas in another group. Jaundice would tend to obscure the diagnosis rather than help to clarify it.

Carcinoma is frequently found in the gallbladder in the absence of jaundice. The earliest and most favorable cases are those in which histopathologic examination after removal of the gallbladder for chronic calculous or noncalculous cholecystitis, reveals carcinomatous changes in the viscus hitherto unsuspected. Another more advanced condition without jaundice, presents the following symptoms and signs in varying combinations, which should raise a suspicion of carcinomatous changes in the gallbladder. An antecedent history of repeated colic over a variable period of time, distressing gaseous indigestion of a chronic, recurring nature, gradually, or suddenly superseded by symptoms of a constant, less severe nature, with that progressive deterioration in weight, strength and appetite characteristic of carcinoma, an enlarged or nodular liver with retention of dye confirming metastatic involvement, and actual or apparent enlargement, firmness and moderate tenderness of the gallbladder. To the absence or marked impairment of function often are added cholecystographic evidences of calculi.

ACUTE AND CHRONIC PANCREATITIS

In this series of fifteen cases there were twice as many males as females.

The age incidence of both sexes fell within the fifth decade, and the males were four years older, on an average, than the females. Diagnosis in this group was based on the history, surgical findings in the pancreas in the absence of other marked gross changes in liver and extrahepatic bile ducts, and eventual good recovery following operation. This latter feature is of significance because it is extremely difficult at times for even the most experienced surgeon to determine from palpatory evidence the exact nature of the pathologic process in this organ. All of the cases were chronic, with one exception, and this patient had an acute gangrenous appendix. The average value of serum bilirubin was 7.5 mg. In no instance was a primary correct diagnosis of chronic pancreatitis made, but in the acute case an alternative correct diagnosis was recorded. In the chronic group were cases of stone in the gallbladder and common bile duct (80 per cent), or carcinoma of the pancreas (13 per cent). In four of these cholecystostomy had been done for the removal of stones, and in several others there were pathologic changes in the gallbladder, in one stones were present. In one case a pancreatic type of diarrhea developed which was treated successfully. In this group, and in the group of malignant lesions in the absence of jaundice, the diagnosis is extremely difficult.

CHOLECYSTITIS WITHOUT STONES

There are seven cases in this series, a smaller incidence than in the series reported by Hartman. The average value of serum bilirubin was 8.1 mg., and in no instance was a correct diag-

nosis made. A diagnosis of calculous cholecystitis (57 per cent), or of choledocholithiasis (43 per cent) was made. There was evidence of associated lesions in the liver, pancreas or common bile ducts in five cases, and in one case the anamnesis and the dilated appearance of the common bile duct at operation made one strongly suspect that a stone had recently passed through the duct. All the patients recovered. One of these cases could have been classified with the preceding group.

MISCELLANEOUS CASES

There were twenty-eight cases in this series, and a variety of entities of infrequent occurrence are included. In cases of jaundice with generalized intra-abdominal carcinoma, the primary source of which could not be determined at laparotomy, gastric carcinoma with metastasis to the liver or common bile ducts, and cholangitis, constitute half of the entire series. It is likely that the pancreas and gallbladder are frequently the site of primary origin. Primary carcinoma of the duodenum, and primary sarcoma and carcinoma of the liver continue to be rare entities, in my experience.

The result of the study of the whole series is summarized in table I.

SUMMARY

Factors giving rise to great difficulty in the successful and expeditious diagnosis of cases of jaundice, under certain circumstances are reviewed.

The most common cause of jaundice

in the cases studied was choledocholithiasis. The most uncommon cause was primary carcinoma of the liver. Error in diagnosis in the former was infrequent (6 per cent).

Calculous cholecystitis without stones in the extrahepatic bile ducts was the second most common cause of jaundice. Correct diagnosis was made in 67 per cent. The chief incorrect previous diagnosis was choledocholithiasis.

A correct primary and alternative diagnosis of carcinoma of the pancreas was made in 92 per cent. The diagnosis of carcinoma of the pancreas in the absence of jaundice is usually exceedingly difficult.

Postoperative traumatic stricture of the extrahepatic bile ducts was the fourth most common cause of jaundice. A correct primary or alternative diagnosis was made in 78 per cent. The chief incorrect primary diagnosis was choledocholithiasis.

The diagnosis of congenital and acquired hemolytic icterus was made preoperatively in 100 per cent. Certain clinical and laboratory data make possible an unequivocal diagnosis in the typical cases.

Primary carcinoma of the gallbladder or extrahepatic bile ducts and chronic pancreatitis, especially in the absence of demonstrable cholecytic disease in the latter, were not often diagnosed correctly prior to operation or necropsy.

Intrahepatic forms of jaundice are frequently erroneously diagnosed as choledocholithiasis or carcinoma of the pancreas.

TABLE I
Element of Error in Diagnosis of Jaundiced Patients (533 Cases)

PATHOLOGIC CONDITION	CASES	SERUM BILIRUBIN, AVERAGE MG PER EACH 100 CC OF BLOOD	CORRECT DIAGNOSIS, PER CLNT		TOTAL	CHIEF INCORRECT PRIMARY DIAGNOSIS	PER CLNT
			PRIMARY	SECONDARY			
Stones in common bile duct	147	91	85	9	94	Cholecystitis with stones	9
Cholecystitis with stones	85	70	67	0	67	Stones in common bile ducts	30
Carcinoma of pancreas	69	174	84	8	92	Stones in common bile ducts	14
Stricture of extrahepatic bile ducts	67	1123	63	15	78	Stones in common bile ducts	28
Congenital and acquired hemolytic icterus	38	45	100	0	100		0
Intrahepatic jaundice	35	120	54	14	68	Stones in common bile ducts Carcinoma of pancreas	26 17
Primary carcinoma of extrahepatic bile ducts	25	160	0	20	20	Carcinoma of pancreas Stones in common bile ducts	52 44
Carcinoma of gallbladder	17	1574	6	35	41	Stones in gallbladder and ducts Carcinoma of pancreas or ducts	59 35
Acute and chronic pancreatitis	15	751	0	7	7	Stones in gallbladder and ducts Carcinoma of pancreas	80 13
Cholecystitis without stones	7	81	0	0	0	Cholecystitis with stones Stones in common bile ducts	57 43
Miscellaneous	28						

BIBLIOGRAPHY

BALFOUR, D C, and ROSS, J W Post-operative biliary fistulas, *Arch Surg*, 1921, iii, 582-594

BOCKUS, H L, SHAY, H, WILLARD, J H, and PESSEL, J F Comparison of biliary drainage and cholecystography in gallstone diagnosis with especial reference to bile microscopy, *Jr Am Med Assoc*, 1931, xcvi, 311-316

EUSTERMAN, G B Carcinoma of the pancreas, a clinical study of 138 cases, *Collected Papers of Mayo Clinic*, 1922, xiv, 206-215

EUSTERMAN, G B Functional tests of the liver a clinical review, *ANN INT MED*, 1927, i, 53-62

GREENE, C H, SNELL, A M, and WALTERS, W Functional tests in the surgical diagnosis and treatment of diseases of the liver and bile ducts, *Jr Lab and Clin Med*, 1931, xvi, 765-774

HARTMAN, H R Jaundice in surgical cholecystitis without stones, *Med Clin No Am*, 1923, vii, 89-95

JORDAN, F M Stones in the common bile duct without jaundice, *Proc Staff Meet Mayo Clinic*, 1930, v, 56-58

JUDD, E S Sequelae and accidents of biliary surgery, *New Engl Jr Med*, 1928, cxcix, 712-716

JUDD, E S, and COUNSELLER, V S The effects of obstructive lesions of the common duct of the liver, *Jr Am Med Assoc*, 1927, lxxxix, 1751-1756

JUDD, E S, and MARSHALL, J M Gallstones in the common bile duct, *Arch Surg*, 1931, xxiii, 175-181

MARSHALL, J R Tumors of the bile ducts, *Surg Gynec and Obst*, 1932, liv, 6-12

McVICAR, C S, and FRITS, W T Clinical aspects of jaundice, *Jr Am Med Assoc*, 1927, lxxxix, 2018-2021

RICH, A R The pathogenesis of the forms of jaundice *Bull Johns Hopkins Hosp*, 1930, xlvii, 338-377

WEIR, J F The diagnosis of jaundice, *Am Jr Surg*, 1932, xv, 494-503

Peptic Ulcer

Early and Late Effects of Parenteral Injections of a Nonspecific Protein: Conclusions Drawn from Experimental Work on the Modus Operandi of the Therapeutic Agent, and on the Etiology of the Lesion Helped by It

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INTRODUCTION

SEVERAL years ago I reported to the American Gastro-enterological Association on a small series of cases of peptic ulcer¹ They had been treated only by means of parenteral injections of milk from which fat and bacteria had been removed Since that time I have followed, with some interest, similar cases and it is now possible to report on a larger series and also upon the duration of relief in the cases so treated

In the preliminary paper I gave an exhaustive review of the literature on the subject Very little has been added to our knowledge since then, so I shall not go further into the matter except to mention the work of Leon Schiff which was reported before the Ohio State Medical Association² during the Spring of 1930 He reviews a series of cases, 27 in number, which have been treated quite similarly to those which I reported upon¹ His results are also quite definite although he obtained complete relief in a smaller per cent of cases—

66 per cent complete cure and 85 per cent complete or partial

METHOD

Ninety-five patients with the history, signs and symptoms, and the roentgenographic and laboratory evidence of peptic ulcer were given intramuscular injections of milk protein* This series included only cases in which the diagnosis was as well established as is possible without biopsy Observations extended over a period of four and a half years Seventy-nine white men, twelve colored men, two white and two colored women were included in the series The ages varied between 21 and 78 years

The patients were allowed to continue on the diet they had been taking prior to their admission into the clinic Therefore, the great majority of them were retained on a regular routine of life because they were also allowed, with few exceptions, to continue in their regular occupations

Control roentgenograms were always used After these were obtained the patients were given their first dose of the nonspecific milk protein Films were

*The nonspecific milk preparation used was Aolin

From the Gastro-intestinal Division of the Department of Medicine of the Johns Hopkins University Received for publication January 16 1932

obtained at the end of treatment. We have in some of the first patients obtained plates many months after the series of injections.

Gastric analyses were obtained before the control films were taken. In the first series of reported cases the gastric acidity was rechecked after some months, as no regularity was observed in the changes of secretion, this check has been largely eliminated.

In the past two and one-half years treatment has consisted of six intramuscular injections of the nonspecific protein on alternate days. If the symptoms were rather slow in decreasing, more than six injections were usually given. The amount used at each injection was always 10 c c.

OBSERVATIONS

The first change noticed in the signs and symptomatology of duodenal or gastric ulcer, following injection treatment is the disappearance of pain. This usually is noted after the second or third injection. Rarely does pain last after the fifth or sixth. It is surprising to see the change of facial expression even in the most chronic cases. Other symptoms such as vomiting, distension, gas, belching, and regurgitation disappear later. A number of the men came in doubled up with pain. The great majority were relieved. Naturally the same amount of relief is not obtained in all cases. However, the large proportion of the patients show a gratifying immediate relief.

In the preliminary paper data were given on roentgenographic changes at various periods after the first injection. At first I had been led to believe that it might be possible to obtain immediate

visualization of decrease of spasm. Films taken one-half hour after the first injection and at the end of the treatment, at a time when in the majority of cases there had been no symptoms for several days, showed little if any changes. Films taken from two to eighteen months after the end of treatment frequently did, however, show definitely less spasm. Occasionally a smaller defect was seen, but in most cases no change was noted.

Films have been obtained on 34 cases two to three years after treatment. Twelve of the cases show a marked improvement as judged by roentgenographic views, others, however, show very little if any deviation from the controls. All cases showing roentgenographic improvement are without symptoms. Three showing only diminution of spasm are clinically well. Some of the patients who are clinically well still have undoubted roentgenographic evidence of ulcer.

The results of treatment on gastric secretion have been reported in detail in the preliminary paper. The conclusion is reiterated: "The immediate and late effects were decidedly different. In the first group, there was an increase of gastric acidity in five of the seventeen cases, an approximate constancy in nine, and a true decrease in three. Of these twenty-one patients, eight were observed after a period of from four to eighteen months. In this group there was an increase of acid in two, an approximate constancy in two and a true decrease in four."

To see any general discomfort follow the injections is a rarity. In five cases there was acute dyspnea with a feeling of suffocation and fright. This was

not accompanied by any marked change in the strength of the pulse and lasted but a few minutes. It was probably due to a leakage of some of the fluid into a vein. To prevent this occurrence the following technic has been worked out. An imaginary line is drawn across the buttock between the anterior superior spine and the sacro-iliac junction. The midpoint of this line is usually situated two to three inches below the crest of the ilium. The needle is inserted by a bold stroke at this point, obliquely downward. Care must be taken to see that it is not in a vein. There are no large veins in this area and I have seen no unpleasant reaction since using this method of injection.

In four cases there has developed local inflammation and swelling of the buttock, similar to an Arthus phenomenon, after the third or fourth injection. In one case a giant urticaria developed eight days after the primary injection. The patient had been receiving injections on alternate days.

It is not an infrequent occurrence to have the patient complain of epigastric pain on the evening of the day on which the injection is given. Constipation is usually associated with the treatment, so much so, that laxatives are given routinely. When occult blood was found in the stools the cases were always followed to note the time of its disappearance. All patients having good results soon presented stools negative to the benzidine test.

I am well aware of the difficulties in the way of making a diagnosis of marginal ulcer after a gastro-enterostomy. In four of the patients such a diagnosis seemed justified. Three of them made excellent immediate recoveries.

Occult blood, which was present in two, soon disappeared. Two of the cases of marginal ulcer had been under strict medical surveillance for some time without relief of symptoms. Under nonspecific treatment both made excellent clinical recoveries.

There have been a number of patients who have relapsed after one series of injections. Most of these can be helped by another course of injections. This is of importance in that group of patients on whom for a variety of reasons, surgery is contraindicated or declined. These may be kept comfortable by repeated courses of the nonspecific treatment. It is especially beneficial in those cases in which the time of recurrence can be guessed by a consideration of previous history. When it is given before this time attacks have been aborted or prevented.

In table I all of the cases have been analysed under two main headings: results noted at the end of treatment and again one to four years after the end of the first treatment. In the latter group several of the patients had been given more than one series of injections and these are grouped under a subheading. Of the 95 patients, 71 received treatment over a year ago and it has been possible to interview 60 of them. Those who received treatment in the past six months have not been analysed for final results. A study of this table shows the interesting fact that the *immediate results* of treatment are superior to the late ones. It also brings out the same relation between the value of treatment and the length of pre-treatment symptoms.

a 84.6 per cent of the patients having had symptoms only a few

TABLE I

The Relationship of Immediate to Late Results Following Nonspecific Protein Injections
Also the Value of Treatment in Relation to the Duration of Symptoms
Prior to Institution of Treatment

		RESULTS AT END OF ONE SERIES OF NONSPECIFIC PROTEIN INJECTIONS			RESULTS 1 TO 4 YEARS AFTER NONSPECIFIC PROTEIN INJECTIONS		
Pretreatment duration of symptoms in years		0 to 1	1 to 5	5 or more	0 to 1	1 to 5	5 or more
Number of cases		26	50	19	18	31	11
PERCENTAGE OF CASES	I Clinical cures	73.1	72.0	52.6	50.0	45.2	36.4
	a With one series of injections	73.1	72.0	52.6	38.9	19.4	9.1
	b With two or more series of injections				11.1	25.8	27.3
	II Improved	11.5	2.0	10.5	27.8	6.5	18.2
	III Unimproved	15.3	26.0	36.8	22.1	48.4	45.5
	IV Coming to operation				11.1	38.8	27.3

months showed rapid clinical cure or improvement

b 74.0 per cent of the patients having had symptoms one to five years showed rapid clinical cure or improvement

c 63.1 per cent of the patients having had symptoms five years or more showed rapid clinical cure or improvement

When we consider the efficiency of treatment instituted one to four years ago in relation to the length of pre-symptoms we note

a 77.8 per cent of those having had symptoms only a few months are still clinically cured or definitely improved

b 51.7 per cent of those having had symptoms for five years or more are clinically cured or definitely improved.

c 54.6 per cent of those having had

symptoms for five years or more are clinically cured or definitely improved

Another point is worthy of note—the cases of long duration of symptoms as a rule require more series of injections than those having had symptoms for but a short time

In order not to over-accentuate the effects of the injections it is well to examine the tables for the relationship between the percentage of clinical cures and clinical improvement one to four years after institution of treatment. Here it may be seen that there is a drop in the number of cases retaining clinical cures in relation to those obtaining complete relief at the cessation of the first series of injections. On the other hand the number of cases which showed clinical improvement alone is greater than in the corresponding group at the end of the first series of injections

DISCUSSION

The classical peptic ulcer gives rise to a series of regularly recurring attacks which come on two, three or four times a year, frequently limited to the Fall and Spring. Each attack is self-limited and during the periods of remission entire good health returns. It is known that the early ulcer of little penetration heals entirely and leaves no scar. As the attacks increase in number or severity, a scar is formed which remains during the periods of remission but which may cause no symptoms. However, in time many extrinsic factors such as secondary inflammation, stenosis, nervous derangement, anatomic or pathologic changes may and usually do cause secondary symptoms which are confused with those of the original ulcer. In fact, it may be that the entire syndrome of the patient is due entirely to these secondary changes.

Considering the mode of onset, the duration of symptoms, the self-limitation of an attack, and the regularity of recurrence, it seems entirely logical to believe that the original ulceration, erosion or congestion may be the result of a reaction of sensitized tissue to a specific antigen. Therefore, the ulcer *per se* is simply an alleergic phenomenon.

If this hypothesis be true it would seem quite likely that we were desensitizing the body against some unknown antigen. Certainly the suddenness with which the signs and symptoms disappeared after the institution of non-specific protein therapeutics via parenteral injection led one to think strongly of this possibility. Consequently the following investigation⁴ has been carried out.

Guinea pigs were sensitized to egg albumen. At various intervals during the development of sensitization (taken as two weeks) different groups were injected with a varying number of doses of intravenous mercurochrome or intramuscular milk protein or both. Each group was controlled with a similar or larger number of pigs. At the end of two weeks all the pigs were given the minimum effective dose which killed a large majority of the control animals. It was found that the agents listed above had the ability to protect a certain proportion of the test animals against death and very frequently against even light to moderate shock. To be effective, the last desensitizing dose must not be given more than 24 hours before the shocking dose. The results may be seen in table II.

Guinea pigs injected intradermally with emulsions of whole bacteria both alive and dead (*Pneumococcus* Type I, *Streptococcus hemolyticus*, and *Staphylococcus aureus* 209) developed sensitization to the same antigen in the remarkably short period of 48 hours. The skin sensitization lasted for at least a month but by that time had diminished. The strongest sensitization was developed ten days after the primary inoculation. Table III gives the results.

Guinea pigs were given intradermic injections of 0.2 cc milk protein in one flank, practically simultaneously with 0.2 cc virulent *Pneumococcus* Type I on the other flank. Twenty-four hours later the milk protein injection was repeated but in a different spot on the same flank. At forty-eight hours the initial injections were repeated but in new areas. Controls were run which

did not receive milk protein Twenty-four hours after the second injection of pneumococcus antigen, there was marked skin reaction in the control animals There was a very much smaller or no reaction in the test animals The difference in the phenomenon may be seen in figures 1 and 2

More recently we have made the interesting observation that it is possible to obtain marked allergic response in the duodenum Guinea pigs were anesthetized with ether By laparotomy 0.1 c.c. of horse serum was injected into the anterior wall of the duodenum The animals were sewed up and placed in clean cages They soon recovered from the effects of the operation and behaved in a normal manner A control series was given 0.1 c.c. of horse serum intraperitoneally Two weeks later the animals were shocked with a minimum lethal dose of horse serum, the dose was determined upon the controls and given into the jugular vein Four pigs which had received injections within the wall of the duodenum, were not given the shocking dose, they were

held as additional controls and killed with ether along with those pigs which survived the minimum lethal dose At autopsy the intraperitoneally sensitized and subsequently shocked guinea pigs showed no lesion in the duodenum The four pigs which had been sensitized within the wall of the duodenum but not shocked showed no lesion in the duodenum Those pigs which had been sensitized within the wall of the duodenum and then given the minimum lethal dose of horse serum showed local areas of congestion in the duodenum and the first portion of the small intestine, in every pig there was a clearly defined engorgement and in some pigs it was quite severe

It seems to us that this may well explain the origin of certain duodenal ulcers

We are now undertaking investigations to determine the possibility of desensitizing the duodenum by the parenteral injection of milk in the somatic musculature

The work on desensitization of both types, specific and nonspecific, points

TABLE II

Percentage of Guinea Pigs Alive and Having No to Moderate Shock Following Various Methods of Nonspecific Desensitization

NUMBER OF DESENSITIZING INJECTIONS	DAYS BEFORE SHOCKING DOSE	PERCENTAGE OF GUINEA PIGS					
		MILK	CONTROL	MERCURIO- CHROME	CONTROL	MILK AND MERCURIO- CHROME	CONTROL
1	1	35	0	54	4	13.3	0
3	7, 5, 1	59.1	0	28.5	0	28.5	0
2	5, 3 and 4, 2	9.5	3.3	20	3.3	9.5	3.3
3	7, 4, 2	0	0	15.4	0	21.4	0
4	14, 12, 9, 7	61	0	8	0	33.3	0
7	14, 12, 9, 7, 5, 3, 1	80	0				

TABLE III
Skin Response in Guinea Pigs to Intradermal Injections of Heat Killed Antigen at Various Periods After an Initial Intradermal Injection With Living or Heat Killed Organisms

ANTIGEN		TYPE OF SKIN REACTION FOLLOWING REINJECTION WITH HEAT KILLED ANTIGEN													
STRAIN OF BACTERIA	CONDITION OF BACTERIA FOR INOCULATION	NUMBER OF PIGS	DAYS AFTER INITIAL INOCULATION												
			1	2	3	4	5	6	7	8	9	10	12	14	16
<i>Living Type I</i>	Living	6	0	++	++	++	++	++	++	++	++	++	+++	++	++
	Heated	6	0	++	++	++	++	++	++	++	++	++	+++	++	++
<i>Str. pyogenicus</i>	Living	6	0	++	++	++	++	++	++	++	++	++	+++	++	++
	Heated	6	0	++	++	++	++	++	++	++	++	++	+++	++	++
<i>Staphylococcus aureus 209</i>	Living	6	0	++	++	++	++	++	++	++	++	++	+++	++	++
	Heated	6	0	++	++	++	++	++	++	++	++	++	+++	++	++

0 = no reaction + = induration 0.8 cm, inflammation 1.0 cm ++ = induration 1.0-1.5 cm, inflammation 1.5-2.0 cm +++ = induration 2.0 cm, inflammation 2.5 cm

Peptic Ulcer

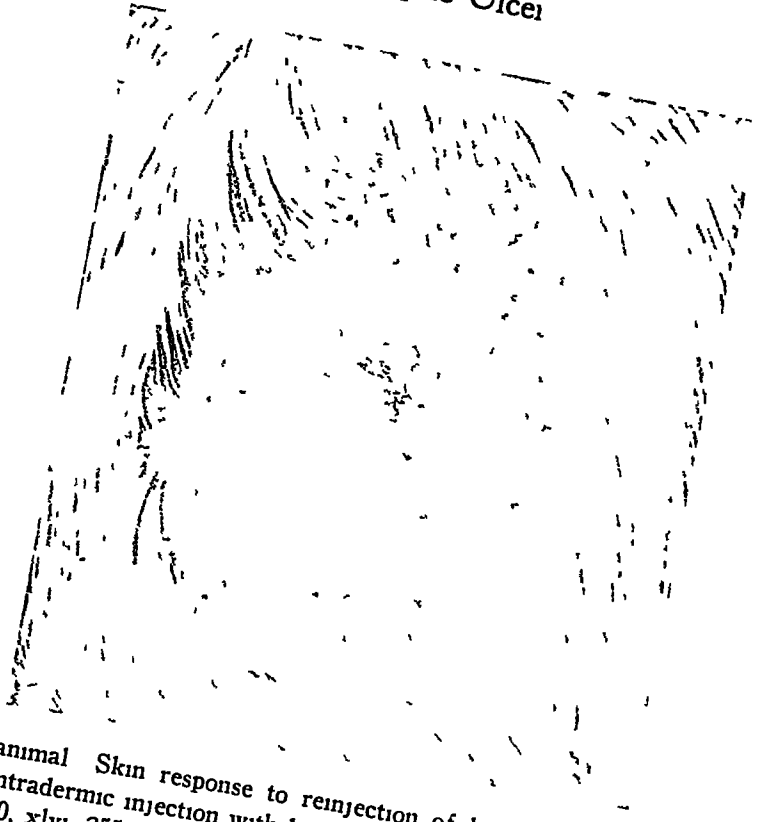


FIG 1 Control animal Skin response to reinjection of heated pneumococcus type I 48 hours after initial intradermic injection with living pneumococcus type I (From Bull Johns Hopkins Hosp, 1930, xlv, 255)

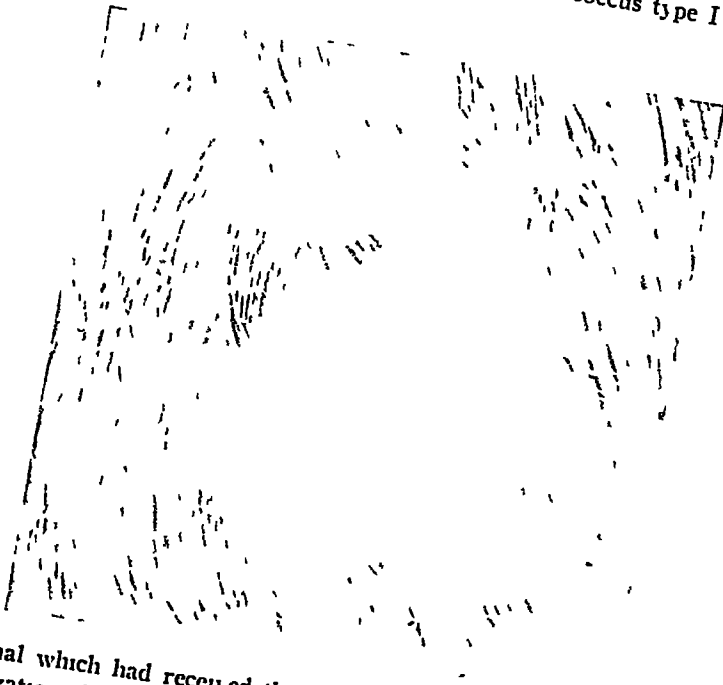


FIG 2 Test animal which had received three intradermic injections of milk protein during period of sensitization Marked diminution in skin response to reinjection of heated pneumococcus type I 48 hours after initial intradermic injection with living pneumococcus type I (From Bull Johns Hopkins Hosp, 1930, xlv, 256)

to the conclusion that the period of desensitization is but temporary and in the nonspecific type it is of short duration. Therefore, if it is true that our results in the treatment of peptic ulcer are due to nonspecific desensitization it will not lead one to expect a cure for a long period of time. Also it should be kept in mind that this form of treatment will have very little, if any, effect against the secondary characteristics of peptic ulcer. It is impossible to expect any relief in the face of a true cicatricial formation which is causing obstruction. On the other hand several cases with partial obstruction have been either clinically cured or improved. In these cases the obstruction must have been due to edema or spasm (secondary results of the ulcer).

Adhesions about, and distortion of the pylorus and duodenum are common secondary changes and no help is to be expected when the signs and symptoms are coming from such a condition.

There are cases, proven at biopsy to be only uncomplicated ulcers, in which the treatment has been of no avail. The obvious explanation in these cases would seem to be that the milk protein had no desensitizing ability.

The German clinicians feel strongly that the beneficial results obtained by this method are brought out by the reaction or shock which follow the intravenous injection of a foreign protein.

As shown above a reaction of such a type in the series is produced only by accident and from the results obtained it seems unnecessary to accept such an hypothesis.

The present method of treatment consists in five to seven injections on alternate days. Depending upon the

type of ulcer and the secondary changes in the stomach, more are sometimes given. Several patients have noticed that a weekly or biweekly injection over periods of weeks will greatly diminish their symptoms. They, however, remain only improved and never become clinically cured, usually they become bored or discontented and drift away.

One of the strongest factors in suggesting this method of treatment lies in the economical side. All but four of the patients were ambulatory, practically all continued with their work and remained on a more or less general diet. I have, however, somewhat changed my views on the latter condition and attempt to keep them on food simpler than they usually consume.

The question of dosage is important. The most satisfactory results have been obtained by giving six or more intramuscular injections of 10 c c each of the nonspecific protein preparation on alternate days. If an Arthus phenomenon or serum sickness develops, treatment must be discontinued or the dosage reduced below the reacting level. At times it is possible to desensitize the patient by slowly increasing the dose, at other times none can be given, another form of nonspecific protein may give excellent results.

There is no doubt of the value of the therapeutics, the results given in table I are quite convincing. The desirability of instituting treatment as soon as possible is definitely shown. Many of the cases had been on a medical treatment for a long time without any benefit being derived therefrom.

In the present light of our knowledge, with the specific antigen or antigen unknown, with the fact that non-

specific desensitization lasts for only a short period of time, it would seem wise to change in some ways the method of treatment carried out in this investigation

- a If the patient presents himself early when the recurrences are appearing at regular times, it would be best to attempt to give a series of injections before the next attack is due. The percentage of clinical cures would most probably be increased. Since good results have been obtained by soft foods, it seems sensible to institute and continue on a white meat, vegetable puree and stewed fruit diet for a considerable period of time and certainly before the next attack is expected to arrive.

If ulcers start as areas of congestion and hyperemia, a soft non-irritating diet may prevent ulcer formation.

- b If the patient presents himself with well marked secondary changes the type of diet outlined above is absolutely indicated. In this manner, food is much more easily transferred through the distorted area and the work of the stomach lessened.

These changes are suggested because

I believe that a greater percentage of the patients will continue the immediate improvement or clinical cure into the group of late results.

SUMMARY

- 1 Intramuscular injections of milk protein have been given to 95 patients suffering from peptic ulcer.

- 2 Of these patients 78 per cent had been greatly improved or clinically cured at the end of treatment. At this time a greater percentage of those whose symptoms had existed for only a few months are clinically cured or improved, that is 84.6 per cent.

- 3 One to four years after treatment 60 per cent of the 60 cases who reported were clinically cured or improved. Of those whose symptoms had existed less than one year prior to treatment 77.9 per cent were improved or clinically cured.

- 4 The majority of these patients had been on a general diet.

- 5 Evidence is advanced that duodenal ulcer in man may be the result of a reaction of sensitized cells to a specific antigen.

- 6 Evidence is also advanced that the therapeutic aid brought about by the parenteral injection of milk protein may be due to a nonspecific desensitization of the sensitized cells.

REFERENCES

¹MARTIN, L. Peptic ulcer. The effect of parenteral injections of purified milk proteins on the symptoms and progress, *Arch. Int. Med.*, 1929, **XLIII**, 299-325.

²——— Ibid, page 303.

³SCHIFF, L., and NORRIS, R. J. Nonspecific protein therapy in duodenal ulcer. (Paper read before the Ohio State Medical Association in May, 1930.) *Jr. Med.* 1931 **LII**, 179-186.

⁴MARTIN, L., and HILL, I. H. I. The effects of mercurochrome and milk protein upon anaphylaxis. II. Development of skin sensitization in guinea pigs in response to intradermal injections of bacteria. III. Milk protein as an inhibitor of skin sensitization in guinea pigs previously injected intradermally with pneumococci. *Bull. Johns Hopkins Hosp.* 1930 **XLII**, 232-258.

The Clinical Diagnosis of Pulmonary Arteriosclerosis

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PULMONARY arteriosclerosis is rather a broad term given to a variety of changes in the pulmonary arteries. Anatomically three types of sclerosing processes are recognized. Atherosclerosis, a senile process which begins rather late in life in the lesser circulation, is always found after 70.¹ It is a part of the generalized atherosclerosis found in the greater system. It is of no particular clinical importance. There are exceptions to that statement. Again, atherosclerosis is found earlier in the pulmonary system accompanying the other two types of sclerosis respectively. Arteriosclerosis in the sense of Jores² is a compensatory phenomenon in which there is a proliferation of the intima and media and in which there is usually involvement of the arterioles. Then there is the inflammatory sclerosis in which syphilis is a specific etiological agent. The French lean toward other infective agents,³ particularly emphasizing the virus of rheumatism. Moschowitz³ insists true arteriosclerosis is always due to in-

creased vascular tension. When found in the pulmonary arteries it is always due to either primary hypertension in this system or is due to increased capillary resistance secondary to mitral disease, congenital heart disease, vascular disease (syphilis), or to increased resistance secondary to diminished capillary beds, as seen in emphysema, chronic inflammatory processes in the lung and pleura, or kyphoscoliosis. Whatever the etiological antecedent, and whatever the variety of changes, if it has clinical significance, there is always associated an enlargement of the right heart. This fact, the right-sided hypertrophy, is of great importance. It is the central corridor for the approach in a diagnostic sense. It is the pivotal fact in making a silent condition swing into a clinically discernible one. For, as this hypertrophy continues, it reaches a stage of imbalance. Decompensation occurs and the latent pulmonary phase enters the cardiac phase—called the “black cardiacs” or sometimes erroneously termed Ayerza’s disease. It would be better to call this stage Ayerza’s syndrome. The usual diagnosis at this stage is “mitral disease” or “congenital heart” or, if there is a history of pulmonary symptoms, the findings in the lungs may cloak the underlying vascular changes.

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Generally speaking, up to 1900 pulmonary arteriosclerosis was a moment of postmortem surprise. Beginning with this century, various observers have claimed a clinical recognition of the condition. Ayerza and Airillaga⁴ in Argentina, Posselt⁵ in Germany, Rogers⁶ in India, Eppinger and Wagner⁷ in Austria, Laubry⁸ in France, Coombs⁹ in England, and a good many others have voiced an antemortem diagnosis and emphasized the possible frequency of its existence.

A tentative schema of the grouping of pulmonary sclerosis is seen in table I. The symptomatology is based on the emphasis placed by the various observers. The symptoms of the acute processes are more or less hypothetical. The French recognize a primary, acute arteritis in the pulmonary system. The acute secondary type must be due always to infection in the right heart and as a rule manifests itself as mycotic aneurysms of the vessels.

Briefly, the clinical bases for the diagnosis of pulmonary arteriosclerosis have been: A delimitation of a heart which resembles a mitral or congenital type, the symptoms of an undue cyanosis and dyspnea not at all commensurate with the clinical findings, repeated

hemoptyses with little evidence of infarct, radiologically, a silhouette of the heart of a mitral or congenital type, with increased hilus shadows, increased vascularity, and visible pulsation of the larger, and sometimes pulsation of the smaller, vessels in the lung field.

A typical schema for diagnosis is given in table II, which gives Posselt's criteria for pulmonary sclerosis associated with mitral disease. To this, I have added a supplementary criterion of Laubry's,⁸ table III, which illustrates the French school of approach and adds considerable radiological minutiae not known at the time of Posselt's writings.

It must be recalled that with the inception of the cardiac phase, progressive cardiac symptoms manifest themselves. By the simple expedient of finding no, or very little, evidence of congestive failure at the base of the lung, when clinically there is a large liver, evidence of ascites and edema, the diagnosis of primary pulmonary sclerosis can be established. This may also be the clinical dividing line between the primary group and the secondary group (table I). In the secondary class the mitral group can be selected from the primary and from

TABLE I
PULMONARY ARTERIOSCLEROSIS

1 Primary No heart lesion	{	a Acute	Hemoptysis—pallor—picture of septicemia or infection
		b Chronic	Hemoptysis, cyanosis (black cardines) picture of mitral or congenital heart—no evidence of congestive failure in the lungs, or very little
2 Secondary	{	a Acute	Mycotic—infection
		b Chronic	Essentially one of heart disease. Hemoptysis with very little evidence of mitral
			Clubbing of fingers rare
			Lung findings present when lung lesions are associated

TABLE II
POSSILT'S CRITERIA (1908) WITH MITRAL STENOSIS

- 1 Physical findings
 - a Increased dullness to the left of the upper sternum and neighboring areas—with pain on pressure or percussion over this area
 - b Exceptionally spreading of heart dullness to the right
 - c The appearance of the pulmonic bulge by X-ray examination
 - d Gradual wandering of apical noises, systolic, presystolic, toward the pulmonic area
- 2 Clinical symptoms
 - a Striking cyanosis, an early sign and long standing compared with the amount of dyspnea or in its absence, or with the amount of stasis or edema
 - b Attacks of dyspragia intermittens angiosclerotica pulmonalis (angina hypercyanotica)
 - c In spite of high grade cyanosis, absence of clubbing of fingers
 - d Repeated hemoptysis without outstanding evidence of infarct

TABLE III
LAUBRY'S CRITERIA (1926)

- Clinical symptoms
- Easily provoked dyspnea
 - Repeated and tenacious bronchitides
 - The repeated appearance of hemoptysis
 - Hemoptysis is more important than cyanosis—which last is more discrete or absent at this stage (early)
 - The cyanosis must be extricated from all other causes capable of producing it and particularly tuberculosis
- Objectively
- Abnormal prolongation of the second sound
 - The persistence of a reduplication with accentuation of the second pulmonic
 - Finally the evidence of a pulmonic soufflé This when present indicates an abnormal distention of the arterial wall
- Radioscopic evidence (fluoroscopic) (Chaperon)
- Two prominent syndromes
- I Venous stasis—characterized by
 - a Increase of hilus shadows whose contours are vague and impossible to define in the inferior portion where the pulmonary veins are lost in the lung fields
 - b By the paradox of an abnormal visibility of the right bronchus
 - c An abnormal bulging of the right auricle
 - d When the pulmonary stasis is pronounced by a diminution of clarity of the lung fields
 - II Arterial hypertension
 - a By an elongation and bulging of the middle arch
 - b By an increase in volume of the pulmonary hilus made up radiologically in the greater part by the arteries whose contours are distinct, easily traceable and whose contractions are copious and more visible
 - c Sometimes by a series of dark trails easily followed throughout the lung fields, animated by contractions like at the hilus and belonging like them to the arterial fields
 - d The phenomenon of the dance of the hilus—only seen twice—possibly due to inflammatory reactions in the hilus

the congenital heart and the heart of chronic inflammatory disease of the lung by the esophagogram. The congenital group and chronic inflammatory group can be differentiated from the others only by their histories, and by the chronic changes in the lungs.

Up to now we have been attempting to diagnose the pulmonary arterio-

sclerosis by the old standards. To these methods I have added an entirely new triad of findings which clinically aids materially in calling attention to the changes in the pulmonary vessels, besides affording a much more accurate and earlier impression of this condition, long before the Ayerza phase has supervened. See table IV.

TABLE IV

A NEW TRIAD FOUND IN CASES WHICH CLINICALLY FIT INTO THE CATEGORY OF
PULMONARY ARTERIOSCLEROSIS

- 1 Palpable pulsation in the intercostal spaces
- 2 A pulmonary souffle heard all over the chest
- 3 The dance of the diaphragm a fluoroscopic finding which consists in a down and up movement of the diaphragm synchronously with systole and superimposed on its respiratory movements

This triad is based on the assumption that, with increased arterial pressure and with the usual accompanying dilation in the larger and medium sized vessels, the increased volume of blood, with increased force, entering the lung would make the lung pulsate as a whole very much like the expansile pulsation of a congested liver in tricuspid insufficiency, or like the pulsation of a liver in aortic insufficiency when there is a marked water-hammer effect in the hepatic arteries. In a case of mitral disease which under the fluoroscope had exquisite pulsation of the pulmonary arteries well out in the lung areas, palpation of the interspaces gave a distinct impulse, not as strong as that felt at the apex but definite enough so that students were able to feel it. This impulse is best felt in the second interspace to the left and right of the sternum, laterally in the interspaces in the mid-axillary lines, and posteriorly in the lower interspaces. Sometimes it can be felt in the interscapular areas. If this were true it occurred to me that there might be a vascular bruit due to the deformity of the pulmonary vessels. This proved to be so in this test case. The bruit is vascular, it must be differentiated and disassociated from cardiac noises transmitted by the chest wall. This bruit is heard all over the chest but can be most clearly heard in the left second interspace, in the right second interspace, and over the whole

right side, particularly since the cardiac noises are less heard on that side. This bruit resembles the noise heard over a placenta, or over a highly vascular and enlarged spleen or pulsating liver. Again it was argued that if a lung pulsated as a whole to the extent that it was palpable through the chest wall it might be possible to see this effect on the diaphragm. Again this case revealed this phenomenon. Under the fluoroscope, particularly on the right side, following a deep breath, the down-and-up movement of the dome can be seen during expiration, synchronous with the heart beat. This movement was called the dance of the diaphragm. In some cases the above technic is not necessary. The dance is seen in either phase of respiration.

The radiologist found two cases with pulsating vessels which gave the above triad of findings. The clinician picked up two on physical examination and predicted the radiological findings of pulsating vessels, also the dance of the diaphragm, both of which were confirmed by the radiologist. The significance of these findings in aiding us in the diagnosis of pulmonary artery disease is apparent.

ILLUSTRATIVE CASES

The following cases are reported which illustrate (1) the variations in the arterial lesions (2) the manner of death and (3) the older clinical ap-

proach None of these had applied to them the test of the new diagnostic triad The reason for this is simple—it was not known at the time

Case I A woman, age 31, following the birth of her child four years before, complained of weakness and dyspnea There had been swelling of the feet, ankles and abdomen the last six months There had been occasional blood-streaked sputum For two years she had been hoarse Her family history is negative Her own gives a record of malaria She has been amenorrheic for two years She had been diagnosed mitral disease with coronary insufficiency Her physical examination gave the usual evidence of congestive failure with more cyanosis than usual and no evidence of moisture at the bases of the lungs In the interscapular area on the left at the level of the third spinous process there was a visible and palpable pulsation and a marked systolic bruit Radiologically the silhouette showed massive right-sided hypertrophy, a marked pulmonic bulge, and enormously dilated pulmonic arteries at the hilus which were seen to pulsate under the fluoroscope There was increased hemoglobin and red cells The Wassermann test was negative The electrocardiogram showed right preponderance A diagnosis of congenital heart disease with patent ductus arteriosus was made, the physical signs in the interscapular area being considered corroborative evidence

Postmortem, the case presented the usual signs of congestive failure The heart weighed 425 grams The hypertrophy was confined to the right ventricle which showed extreme hypertrophy and dilation No changes were noted in the valves The foramen ovale was not open and there was no indication of the presence of a ductus arteriosus The coronary and the root of the aorta were smooth The root of the pulmonary artery was also smooth

The right lung weighed 400 grams Crepitation was present throughout There were no pleural effusions but there were a few areas of slight consolidation in the apex The pulmonary artery which opened was found to be dilated and the wall of yellow raised

intimal thickening The thickened areas were arranged in spots, particularly about the orifices of the branches of the artery The pulmonary artery was extensively dilated It had a large caliber far into the lung in its many branches On section, microscopically, a few active areas of tuberculosis were found in the apex The small arteries showed a marked intimal thickening which had the appearance of being proliferative in character, the lumina of many of the small arteries were almost completely closed In the larger arteries there was a marked atheromatous condition The left lung weighed approximately the same as the right and showed a similar condition in the pulmonary vessels

Comment This was a beautiful case of primary pulmonary arteriosclerosis Being our first case, we were led into the usual error of calling it a mitral or congenital heart disease (See figures 1 and 2)

Case II N J, female, age 27, complained of dyspnea, edema of legs, and prolonged uterine bleeding Her family history was negative The patient has had weakness on exertion since she was 15 years old Three years ago there was hoarseness and the sputum at times was blood-tinged Physical examination on two admissions gave the following data Heart enlarged to the right and left, and a mitral murmur The chest was clear, the liver down There was pitting edema of the extremities There was marked cyanosis, and a dark brown pigmentation over the face, mouth, extremities and body Laboratory examination Hemoglobin, 108 per cent, red blood cells, 5,000,000 plus, white blood cells, 15,000, polymorphonuclears, 80 per cent Stool and urine examinations were negative The basal rate was normal The Wassermann test was negative Blood pressure 90/80 to 160/100 X-ray studies showed a massive right heart, no esophageal displacements, no pulsation of the pulmonary vessels, or any involvement of the lungs Electrocardiogram showed right preponderance A diagnosis was made of mitral disease, congenital heart, Ayerza's disease The patient died in convulsions

Postmortem findings The heart weighed 360 grams. The left auricle and ventricle were normal, the right auricle and ventricle were greatly dilated and showed moderate hypertrophy. A careful search was made for anomalies, but none were found. The pulmonary artery was dilated, apparently larger than the aorta. The tricuspid and pulmonary valves were enlarged. The root of the aorta was smooth except for an occasional yellowish plaque.

The right lung weighed 430 grams, the left 315 grams. There was a moderate, yellowish sclerotic thickening of the larger branches of the pulmonary artery. There was dilation of some of the middle-sized branches. The veins were normal. There was

an old Ghon tubercle beneath the pleura of the right lower lobe. The aorta was small and smooth. Many sections of the lung examined for evidence of sclerosis of the arterioles proved negative.

Comment This case was a clinical replica of the first. The points of similarity were (1) weakness and dyspnea over a long period, (2) cough with sputum at times hemorrhagic, (3) cyanosis with increased hemoglobin, (4) pigmentation, (5) decompensation *without evidence of congestive failure at the base of the lung*, (6) vocal cord involvement, (7) massive enlargement



FIG 1 Gross specimen of lung of Case I, showing atherosclerosis and dilation of large vessels

of the right heart, (8) pulmonary artery dilation, (9) evidence of previous or present tuberculosis. The difference lies mainly in the pulmonary artery. The first case had peripheral arteriolar sclerosis with dilatation and atherosclerosis of the larger vessels. The second had dilatation of the larger vessels with some sclerosis, but the peripheral vessels were normal. In the first case the hypertrophy of the right heart can

Case III L. K., age 65, female. This patient led an active life. There is a history of asthma and bronchitis for many years. For three years there had been progressive heart failure with no response to any type of therapy. Edema was controlled for a long time by ammonium nitrate and salyrgan. The diagnosis of pulmonary arteriosclerosis was made by exclusion because of the progressive character of the failure, the marked cyanosis and the lack of evidence for coronary disease. There was edema, ascites, enlarged liver, but the lung bases were clear, that is,

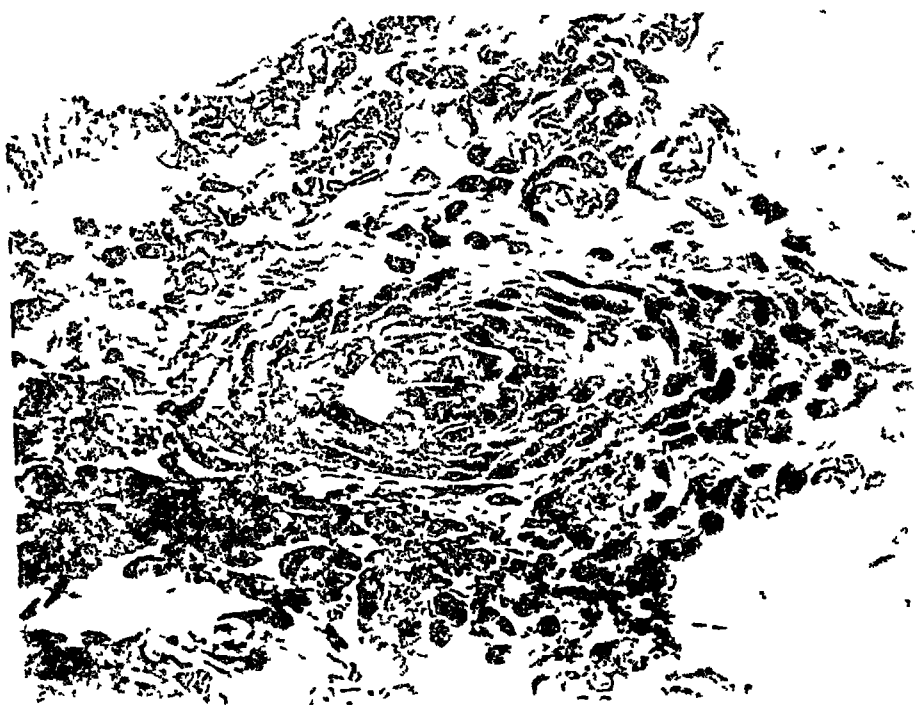


FIG 2 Obliterating sclerosis of arteriole in periphery of lung, Case I x300

be easily explained by the increased arterial tension. In the second case we must explain the right-sided hypertrophy on some other basis. I venture the following. The loss of elasticity in the dilated vessels threw an extra burden on the heart which caused its hypertrophy. This does not apply particularly on the left side. There are many compensatory factors on the left side which do not obtain in a simple system like the lesser circulation

until fluid appeared toward the end. There was radiological evidence of old healed tuberculosis of the lung with old pleuritis.

At postmortem examination the heart weighed 575 grams. There was hypertrophy of both ventricles, with marked dilatation of the right auricle and ventricle. The coronaries were sclerotic but patent. The aorta showed marked sclerosis extending to the iliacs. There was marked sclerosis and dilatation of the pulmonary arteries. On microscopic section the peripheral vessels of the lungs showed sclerosis also.

Comment Occasionally one finds

sclerosis in both systems. Here the extensive change in the pulmonary vessels was striking. The sclerosis might be considered as a senile process. In any event, the *factor* of the sclerosis of the pulmonary vessels with the dilatation is strongly emphasized as a cause of heart failure in this case.

*Case IV** J. S., male, 73. This patient gave a history of onset with an acute respiratory infection with cough, fever and pain in the chest which rapidly subsided. This was followed by attacks of dyspnea and edema of the extremities. These symptoms continued for two years, when he entered the hospital with a particularly severe attack.

*Previously reported by Dr. A. R. Hall of St. Paul, at the Minnesota Academy of Medicine, 1927. I again thank Dr. Hall for permission to use this case.

of dyspnea and cyanosis. His temperature was normal, the heart sounds were clear. A diagnosis of asthma and bronchitis was made. The patient died suddenly.

At postmortem examination the heart weighed 710 grams. The left ventricle was slightly enlarged. The right ventricle was much enlarged in size. There were no anomalies, acquired or congenital. A thrombus was present in the pulmonary artery, 3 cm. above the pulmonic valves. This thrombus was old and organized and on this a fresh thrombus occluded the vessel completely. All the branches of the pulmonary artery were occluded with thrombi attached to their walls and the vessels appeared thickened throughout. Microscopically the vessels showed marked hypertrophy of all the coats. The vasa vasorum were dilated and filled with blood, giving the appearance of an attempt at collateral circulation. The smaller vessels showed obliterating sclerosis.

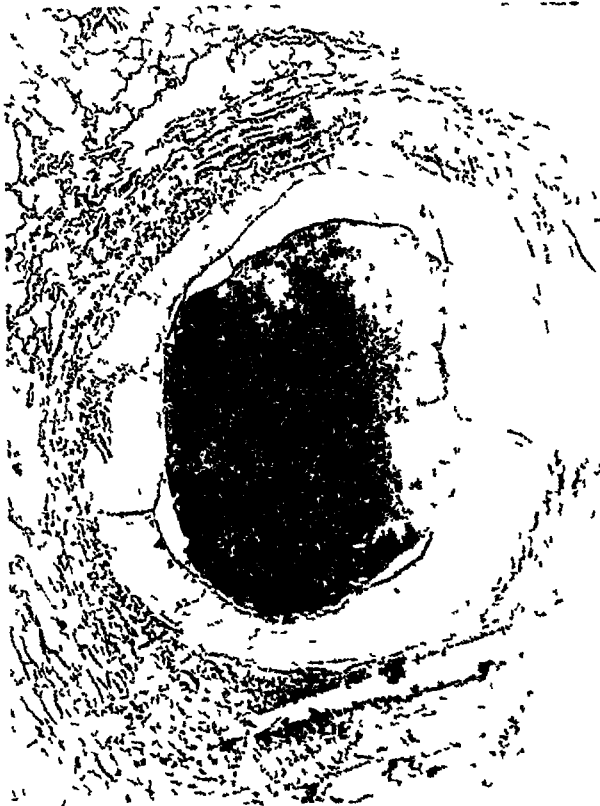


FIG. 3. Thickening of vessel walls and organizing thrombus in a vessel of moderate caliber. Note the reaction in the vasa vasorum. Case IV. x60.

Comment This case is included because of the age of the patient and the manner of death. Complete occlusion of the pulmonary artery by a thrombus is not common in arteriosclerosis of this vessel.

The following four cases are very briefly detailed with silhouettes because they represent a group in which we have applied the new triad as well as the old criteria in coming to the conclusion that we are dealing with pulmonary arterial disease.

Case I Female, age 26, entered the hospital for a minor orthopedic operation. She gave a history of repeated attacks of tonsillitis but not rheumatism. There had been attacks of cardiac embarrassment since her fifteenth year. A diagnosis of mitral disease

was made, which was verified by X-ray (figure 5), including a positive esophagogram. Under the fluoroscope the pulmonary vessels were seen to pulsate far out in the lung fields. It was on this case that we worked out the triad of physical findings.

Clinical diagnosis Mitral disease with pulmonary arteriosclerosis.

Case II I S, female, age 14 (Figure 6). There was a history of whooping cough at 5 weeks (?) from which 9 months was required for convalescence. At 3 years she had scarlet fever with kidney involvement. Heart symptoms were noted at 5 when she had smallpox. She began school at 6, at 8 she was easily fatigued on slight exertion. She had had several periods of long rest in bed. Briefly her physical examination showed some cyanosis, varying cardiac noises, *lungs clear*. Her X-ray findings showed a congenital type of heart with pulsating pulmo-



FIG. 4. Proliferation and edematous thickening of the intima of a much smaller vessel. (G. & V. 734)



FIG 5 Teleoroentgenogram of Case V Typical mitral configuration The oesophagogram was positive Cardiac condition Mitral stenosis

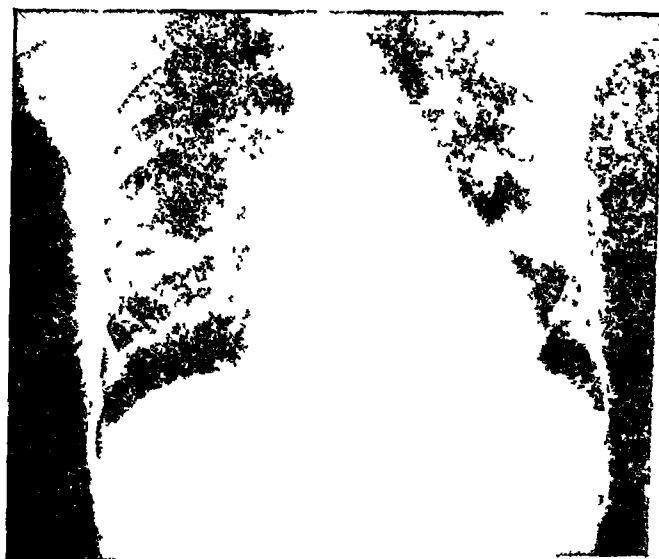


FIG 6 Teleoroentgenogram of Case VI Note enlarged heart with typical pulmonary bulge The oesophagogram was normal No cardiac condition

nary vessels in the lung fields. In attempting to find our triad in this child, she gave beautiful evidence of pulsation of the intercostal spaces, an exquisite pulmonic soufflé and, under the fluoroscope, the dance of the diaphragm.

Clinical diagnosis Primary pulmonary arteriosclerosis.

Case III M. N., male, 12 (Figure 7). This boy had a severe bout of rheumatism. There was a pancarditis. The pericarditis and effusion were very severe. There was a slow recovery with restoration of normal blood findings and weight but the tachycardia persisted. He likewise exhibited our triad of findings. The pulsation of the vessels and the dance of the diaphragm were predicted in his case by the clinician.

Clinical diagnosis Mitral disease, adherent pericardium, pulmonary arteriosclerosis.

Case IV Female, age 24 (Figure 8). There was a history of the diagnosis of a

congenital heart lesion for 12 years. Since that time the patient has lived a restricted life. There were weakness, dyspnea and cyanosis. Lungs were clear. The heart was not much enlarged, there was a typical thrill and systolic murmur at the second interspace. This patient likewise gave the evidence of increased pulmonary circulation according to our physical tests. At the first thought one would wonder how stenosis would permit the factor producing sclerosis to operate, furthermore, with stenosis how the physical signs found in the chest in this case were possible. In answer to this question I can only state that Posselt¹⁰ in his 127 cases of pulmonary arteriosclerosis found 4 with pulmonary stenosis.

Clinical diagnosis Pulmonary stenosis, pulmonary arteriosclerosis.

Comment With the evidences of a mitral or congenital heart and the rad-

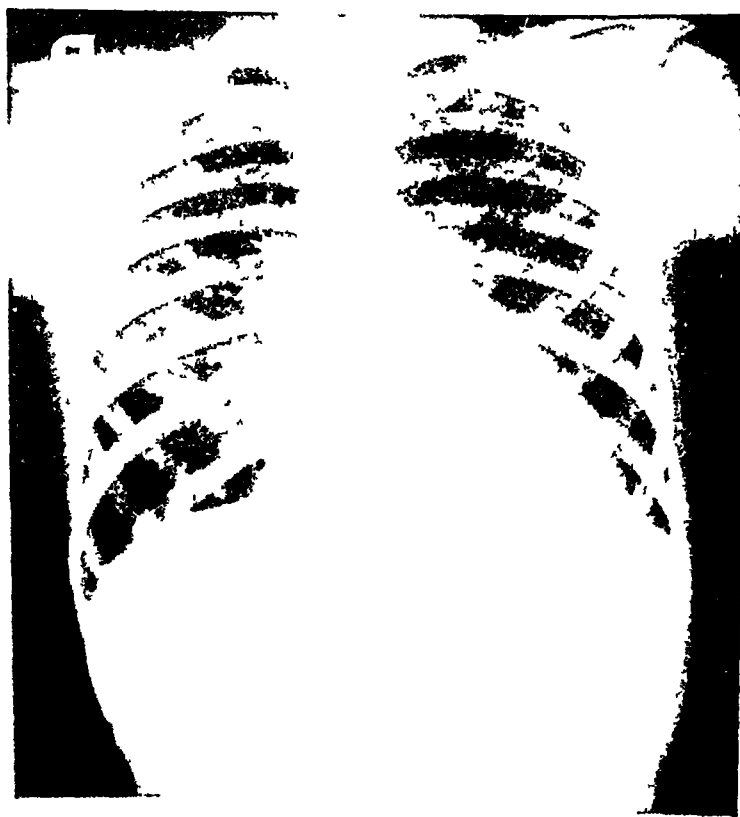


FIG. 7. Fluoroscopic view of Cx. VII. Note the enlargement of the heart in both directions. The cephalogram showed the characteristic impingement due to a dilated left ventricle. Cardiac condition, rheumatic heart, mitral stenosis, adherent pericardium.

iological evidence of pulsation of the pulmonary vessels, and the corroborative evidence of this new triad of findings, it is reasonable to assume that we are dealing with increased arterial pressure in the pulmonary vessels. And, furthermore, that, with such increased pressure, changes in the vessels have occurred which can be included in the clinical diagnosis of pulmonary arteriosclerosis.

SUMMARY

A new triad is added to the old criteria for the diagnosis of pulmonary arteriosclerosis. With this new triad an earlier diagnosis of pulmonary arteriosclerosis is possible—long before the cardiac phase has been reached. Dilatation with consequent loss of elasticity of the pulmonary vessels may be a factor in the right-sided hypertrophy



FIG 8 Teleoroentgenogram of Case VIII showing the typical pulmonic bulge. Oesophagogram normal. Cardiac condition pulmonary stenosis.

REFERENCES

- ¹LJUNGAHL, MALTE. Untersuchungen über die Arteriosklerose des kleinen Kreislaufs 1915, Verlag von J. F. Bergmann, Wiesbaden.
- ²JORRES, L. Handbuch d. spec. path. Anat. u. Hist., 1924, II 608.
- ³MOSCHCOWITZ, F. Hypertension of pulmonary circulation, *Am. Jr. Med. Sc.* 1927, *CLXXV*, 388-406.
- ⁴BRILLACQ, F. C. Sclérose de l'artère pulmonaire secondaire à certaines causes pul.

demic proportions and reached its height in the Sacramento Valley between July 11 and 20. Although cases were seen throughout California, serious outbreaks were reported principally from the Sacramento Valley and Southern California. Localized outbreaks have been observed in Nevada and Arizona. For a week or two the malady would rage in a certain section, then subside only to reappear in the same district. It is of interest that the horses of most of the farms, which had one or many cases of encephalomyelitis during 1930, remained well in 1931 despite the fact that they were located in districts which suffered heavily during the most recent epidemic. As a rule only one horse in ten showed symptoms of the disease in the 1930 outbreak and rarely more than one or two animals of a group became affected. However, during 1931 higher proportions than this occurred. Thus on one ranch, five of twenty-two animals were infected, on others seven of eight (6 deaths), three of nine, and five of fourteen respectively were observed. This peculiarity has been explained on the hypothesis that many horses contract the disease in such a mild form that it is not recognized. Again with the onset of cooler weather, in October, 1931, the disease disappeared. A non-official but cooperative canvass among practicing veterinarians in the stricken districts elicited a total of 2,416 cases. Supplemented by additional reports from various other sources it is estimated that early in 1931, 5,580, or 25 per 1,000, of the horse population contracted the disease. The average mortality was 47 per cent. Therefore during 1930 and 1931 approximately 6,000

horses succumbed to a form of encephalomyelitis which is apparently identical with the so-called "cerebrospinal meningitis" reported from various parts of the United States during the past 70 years. In the west Central States this infection caused heavy losses in 1912 as the so-called "Kansas-Nebraska horse plague". It has frequently been confused with "forage poisoning" and "equine botulism". During the past 2 weeks (March, 1932) reports have been received that the disease is again active in the San Joaquin Valley and in Southern California and it is anticipated that with the onset of warm weather the infection will reappear in epidemic form.

Stallions, as well as geldings and mares, and suckling colts, even aged horses, are susceptible. As a rule only animals kept on farms in more or less cultivated districts have contracted the disease. Nothing definite is known relative to the spread of the disease from farm to farm or how it is introduced into a community or why it occurs in *periodic cyclical* recurrences in extensive outbreaks within a year. Since the virus circulates in the blood, the rôle of flies or other biting insects deserves experimental consideration. In many ways, the equine malady shows a behavior analogous to human infantile paralysis. It is therefore not unlikely that the spread is due principally to unrecognized carriers. However, the infection may possibly be carried by food or water which has at some time been contaminated by the carriers or the diseased animals. Certain technical difficulties have thus far rendered a search for carriers impractical.

CLINICAL SYMPTOMS

The period of incubation in the spontaneously contracted disease is difficult to estimate although a few observations indicate a lapse of from one to three weeks between exposure and readily recognized symptoms. Under experimental conditions and especially with massive intracerebral infection the incubation time is on the average eight days and may be as short as three days.

Preceding the onset of the acute symptoms which attract attention, the temperature is found to vary from 37.2° to 41.1° C. Unwillingness to be led, lack of spirit, slightly incoordinated gait, abnormal position of the limbs, failure to respond when called, or in unbroken colts, failure to run when approached are some of the premonitory signs which may rapidly be followed by more pronounced manifestations of the disease.

In severe cases, the horses stagger, fall and are unable to get up when pressed to do so. They may lie on their sides. Convulsive or swimming motions are common and cause, as a rule, severe bruising of the head and limbs. In the advanced stages, the animals are relatively quiet. The pulse and respiration are usually accelerated and towards the end arrhythmic. Cutaneous hyperesthesia of the neck may be followed by anesthesia. The examination of the blood reveals a polycythemia (due to dehydration) a slight leucopenia and a raised icteric index. The findings in the urine are essentially normal. The conjunctiva is always injected and frequently icteric or grayish, being studded with petechiae and ecchymoses. Motor disturbances in

the innervation centers of the cranial nerves are usually present in more severe cases. Inability to swallow, facial paresis, fibrillar spasms of the muscles of the face and limbs, continuous or periodic grinding of the teeth, rarely amaurosis, râles in the throat and a foul smelling breath and paresis of the lips are characteristic of advanced cases. Such animals may succumb to the infection in from three to eight days or, since the prognosis is hopeless, due to complications such as pneumonia, they are usually destroyed for humane reasons.

Two clinical types are common in the milder cases—the sleepy and the walking type. In the former, the horse may lean with a drooping head against supporting objects in a drowsy somnolent state, occasionally grinding the teeth, or yawning. A peculiar looseness of the lips or a twisting of the upper lip to one side may be noted. The walking type is characterized by circling motions. Such cases may follow close to the fence and only change direction when they come in contact with a turn in the fence or other obstacle.

In approximately 10 to 20 per cent, recovery within a few days is uneventful although the animals may have a nasal discharge for several weeks and exhibit a slightly incoordinated stiff gait and a marked loss in weight. Although the available data are incomplete it has been gradually recognized that many horses fail to regain their original vigor and strength.

GROSS AND MICROSCOPICAL
PATHOLOGY

The anatomical lesions found on autopsy of animals sacrificed before

the onset of complications, are insignificant. Aside from a general icterus of varying degrees of intensity, succulent lymph-nodes and slight parenchymatous changes in the liver and kidneys no gross lesions are found. No enlargement of the spleen has been noted. The spinal fluid may be markedly increased and show a lympho- and leucocytosis (12 to 30 cells per c mm). As a rule the brain and cord are moist and injected irrespective of the advanced dehydration of the tissues which may be present.

Microscopically, the most conspicuous changes consist of hemorrhages around the vessels of the olfactory bulbs and the brain stem, and edema and infiltration of the perivascular sheaths and spaces by mononuclear and polymorphonuclear cells. This cuffing of the veins and arteries is variable in intensity but is always pronounced in the advanced cases of the disease. Scattered patches of infiltration in the gray and white matter are common. It may be very pronounced in the vicinity of the innervation centers of the facial nerves and throughout the entire cord. Areas of infiltration are also noted in the semilunar and peripheral ganglia. However, the distribution and intensity of the inflammatory foci differ from that commonly seen in typical Borna disease. Nuclear inclusions, of the character described as typical of Borna disease by Joest and Degen, have not been observed in the specimens obtained in 1930. However, since Dr. J. A. Howarth has found peculiar intranuclear corpuscles in the ganglion cells of the hippocampus of brains secured from the 1931 epidemic, it is deemed advisable to withhold final con-

clusions as to these until a more detailed search has been completed.

ETIOLOGY

As already mentioned, the disease was originally attributed to the pathogenic action of various organisms or to the toxin of *Cl. botulinum*. Through the studies of Meyer, Haring and Howitt⁶ of California, and Record and his associates⁴ of Nevada, evidence has been furnished that the American encephalomyelitis is produced by an ultramicroscopic organism. The virus has been demonstrated in the brain tissues of two of nine horses ill from the spontaneously contracted disease in the 1930 epidemic. It has been passaged through various animals, in particular, guinea pigs. With an improved technique and the selection of the guinea pig as the most susceptible laboratory animal the virus has been recovered in four of eight cases studied during the 1931 outbreak. The failure to demonstrate the infective agent in every case is probably due to the uneven distribution of the virus in the brain tissues and the process of autosterilization which is apparently in progress at the time the disease is clinically recognized. In the course of one transmission experiment only one of eight guinea pigs injected intracerebrally with the brain emulsion of a field case developed symptoms and succumbed to the virus infection. The chances of recovering the virus are greater when the brain stem is tested during the first or second day of the clinical disease than when the material is secured from a horse which has been ill for a longer period.

Blood cultures prepared from 12

horses in various stages of the disease have remained free from readily cultivable micro-organisms. The spinal fluid of four cases sacrificed on the second day of the visible disease remained sterile, while that of 12 horses sacrificed or dead on account of encephalomyelitis gave cultures of hemolytic and nonhemolytic streptococci. These organisms proved to be nonpathogenic to small laboratory animals and horses and are considered as secondary invaders.

Enrichment cultures of pieces of brain and spinal cord in blood broth yielded α and β streptococci in four of ten horses so examined. In every instance the horse which furnished the positive cultures had been ill for some time or had died. The virus was demonstrated in the brain tissues which gave no visible growth on culture media free from living cells.

ANIMALS SUSCEPTIBLE AND MODES OF INFECTION

Guinea pigs, rats, rabbits, mice and monkeys (*Macacus rhesus* and *cynomolgus*) are all susceptible. The young guinea pig, weighing 250 to 300 grams, is probably the most susceptible laboratory animal, the incubation time varies from one to three days after inoculation by the intracerebral route. A sharp febrile reaction, 40° C and above followed within two days by a subnormal temperature, announces the progress of the infection which manifests itself in the form of flabbiness of the abdomen, weakness, salivation, humped cat-pose or inability to rise, tumbling motions, fibrillar tremors of the limbs and paws, loss of weight and death between the fourth and sixth day. Guinea

pigs may be infected by the cerebral, intraperitoneal, subcutaneous and intracutaneous routes. With a potent virus the infection is regularly fatal. Successful infections followed the nasal instillation of virus in the guinea pig and rabbit but not in the horse. Feeding of virulent material to guinea pigs has in the few experiments performed failed to infect. In fact, continuous passage through guinea pigs enhances the virulence for this rodent. During the execution of the experiments, normal guinea pigs have been in intimate contact with infected animals. Thus far no infections by cohabitation have been observed.

Rats are likewise susceptible. The infected animals show general weakness, incoordinated motions and a crusty nasal discharge. Death follows in from six to eight days.

Young rabbits are susceptible to infection by the intracerebral, intraocular, intravenous and nasal routes. The disease is not always fatal. Some rabbits may have fever of short duration, usually from the second to the fourth day after the injection, if chloroformed at this stage the virus may be demonstrated in the brains. In the fatal infections the fever subsides just as in the guinea pig and is followed by general weakness accompanied by vain efforts to rise, abnormal positions and tremors in the extremities are regularly followed by death on the fifth to the tenth day. Passage of the virus through rabbits does not diminish its pathogenicity for guinea pigs, monkeys and horses.

Although mice are apparently less susceptible to infection than rats or guinea pigs they may be infected by

intracerebral or by intraperitoneal routes, provided, in the latter procedure, the central nervous system is injured by an injection of a starch solution. Death on the seventh or eighth day may follow a period of lethargy.

Monkeys are readily infected by the intracerebral route in consecutive passage, with virus obtained directly from horses spontaneously ill of the disease or from experimentally infected rabbits and guinea pigs. The incubation in 18 monkeys has averaged four to six days, and the time between infection and death eight to ten days. Preceding the onset of visible symptoms the body temperature rises above 41°C . Extreme weakness, unsteadiness, somnolence, trembling of the head and extremities, muscle spasms, facial paresis, desire to chew or to gnaw, and a swaying gait to one side may be followed by inability to rise and later by death. The characteristic perivascular and parenchymatous infiltrations are found in the central nervous system. Recovery has been noted in one of the 18 monkeys successfully infected. The virus after passage through the monkey does not lose its virulence for the horse or guinea pig.

Nineteen horses have successfully been infected by the intracerebral and one by the intra-ocular route. Two equine animals contracted the disease following the subcutaneous injection of a total of 12 grams of brain substance from spontaneous cases of encephalomyelitis observed during the month of July, 1931. As a rule, however, repeated inoculations lead to immunity. Since many of the horses have been sacrificed in order to obtain the maximum amount of virus, only the early symp-

toms have been carefully studied. The incubation time following intracerebral injection of the virus varies from three to eight days. As a rule the onset of visible signs is preceded by a rise in temperature of from 2° to 3° , varying from 39° to 40.5°C . However, a febrile reaction may not be recorded. Accompanying the fever, slight psychic depression and incoordination in gait may be noted. On the fifth to the tenth day the animal may stagger, grind its teeth, appear dull, somnolent, or aggressive and try to bite. The symptoms of anorexia, defective deglutition and inability to rise become more marked and the animal dies between the sixth and fifteenth day. In general, symptoms and anatomical findings are indistinguishable from those of the spontaneous disease. During 1931 a few horses were found to resist infection by the intracerebral route. The hog and chicken appear to be resistant to infection.

CHARACTERISTICS OF THE VIRUS

The virus passes readily through bacteriological filters such as the Berkfeld V and the Seitz filters. Guinea pigs as well as horses have been successfully infected with such filtrates. In this respect the virus differs from that of Borna disease. There is some evidence that the virus passes through a 30 but not a 35 or 40 per cent collodion ultrafilter. Experiments on guinea pigs indicate that the virus is active in a dilution of 1:1,000 of brain suspension, but not in a dilution of 1:10,000. In the dry state the virulence is retained for at least $5\frac{1}{2}$ months and when kept frozen remains active for five weeks. It is very resistant to glycerin. Held

in neutral 50 per cent glycerin at 41° C the brain tissues secured from an experimentally infected horse remained virulent for 12 months

Miss B Howitt⁵ has shown that the whole blood or the serum from the peripheral circulation and the heart blood of experimentally infected guinea pigs and monkeys collected during the febrile period may contain the virus. In one horse infected by the intracerebral route the virus was demonstrated in the blood with the onset of the febrile reaction (third day after the inoculation). Repeated unsuccessful attempts were made in 1930 and in 1931 to find the virus in the venous blood of horses spontaneously ill from encephalitis. The blood was re-injected subcutaneously into horses or tested on guinea pigs. Experiments to demonstrate the virus in the blood of several experimental horses examined early during the febrile rise of the body temperature were also unsuccessful. The failures may be attributed to the great dilution of the virus in the horse and to the technical procedure which permits only a relatively small amount of blood to be tested on a guinea pig by intracerebral or intraperitoneal injection. As soon as suitable methods of concentration by absorption have been worked out the search for the virus in horses will be resumed. Thus far it has been recovered only from the cerebrum, pons, medulla oblongata, spinal fluid, spinal cord and one lymph node (Records⁴), but not from the liver, spleen and kidneys of the horse. On the other hand Miss B Howitt has found the virus in the peripheral nerves of a monkey and in the salivary glands, spleen, liver and adrenals of guinea pigs, but not in their feces.

IMMUNITY

Veterinarians have reported the recurrence of encephalomyelitis in 16 horses during the 1931 epidemic. A "recurrence probability" of only 0.7 per cent would indicate that relapses are rare and that a clinical attack of the disease is productive of a high degree of immunity. The existence of such a state has been proven in several horses recovered from a spontaneous attack or infections experimentally induced by the intracerebral injection of a very potent virus. Furthermore, in the course of infection-experiments on horses purchased at random during 1931, obviously immune animals have been encountered.

Then again, a comparison of the epidemiological data from 1930 and 1931 makes it perfectly clear that the various waves of encephalomyelitis leave behind a horse population powerfully refractory to subsequent infection.

Accompanying the visible epidemic of 1930 carefully recorded at one ranch (with 687 horses and mules, 67 cases and 32 deaths), a much larger invisible immunizing wave must have established the protection which prevented the occurrence of a single case in 1931. The nature of this immunity in the horse is not known since repeated attempts to demonstrate antibodies capable of neutralizing the virus *in vivo* or *in vitro* in the blood-serum of recovered horses have failed. As an emergency the use of convalescent serum was recommended during the epidemic of 1930 and 1931. Its utter lack of therapeutic value was doubtless due to the absence of protective antibodies in such sera. On the other hand it is im-

portant to note that the sera of rabbits, guinea pigs and monkeys contain specific antiviral substances which, according to Miss B. Howitt, protect laboratory animals. The potency of such sera, in particular those of rabbits, can be increased by repeated subcutaneous injections of virus. These "hyperimmune" sera will protect guinea pigs against a fatal intracerebral or nasal administration of the virus if given one or even four days preceding the infection. These experiments have clearly shown that a therapeutic effect can be expected only during the febrile period when the virus is not as yet fixed in the central nervous tissues. These observations and other theoretical considerations prompted the preparation of "hyperimmune" sera in 17 horses which had either recovered spontaneously or had passed through an unrecognized infection following the intracerebral administrations of small amounts of virus or the subcutaneous injection of large quantities. The immunity of the treated horses was established by one or several intracerebral test injections of the virus. Although the majority of the horses survived these drastic tests only four, upon prolonged immunization furnished sera which neutralized the virus with any degree of certainty *in vitro* and *in vivo*. The pooled serum of these horses has been used intravenously in amounts varying from 500 to 1 000 cc. on 39 horses in various stages of the disease. Thirty animals made a rapid and uneventful recovery, while nine, or 23 per cent (average mortality during 1931, 47 per cent), died or were sacrificed on account of complications. The mortality in a group of 13 horses treated by Dr. E. A. Howarth early in

the course of the disease was two, or 15.3 per cent. An opportunity may be afforded to evaluate more conclusively these encouraging preliminary results in the course of future epidemics.

Experiments having in view the immunization of horses are few. Twelve horses received subcutaneously 60 cc. of a 20 per cent suspension of virulent horse or monkey brain. The injections were well tolerated in 11 animals. One horse after four injections at three day intervals (48 grams of brain material) developed typical symptoms of encephalomyelitis on the fifteenth day after the first, or the fourth day after the last, injection. The horse died on the fifth day of sickness. For several months the immunized horses, which had been tested by intracerebral injections and had been bled repeatedly six to twelve liters, remained well. Subsequently, seven horses sickened with fever, weakness, depression and anorexia, but had no symptoms indicative of localized involvement of the central nervous systems. These animals succumbed to the acute disease or remained weak for months and finally died unexpectedly. At autopsy a splenic tumor and extensive degenerative changes were found in the liver and kidneys. The nature of the disease has not been determined although a malady resembling it clinically and anatomically has been produced in a horse. Efforts made on small laboratory animals by the subcutaneous injection of spleen and liver tissues secured from one of the rapidly fatal cases have failed. It may be mere coincidence but the disease developed only in the horses injected with brain tissue which contained the encephalomyelitis virus. Several equines, which

served as controls, mingled freely in the same pasture and barn with the treated animals. They have remained well.

Further active immunization experiments have been deferred until Miss B Howitt has completed her study on the immunizing properties of the virus treated by various methods.

CROSS IMMUNITY BETWEEN THE VIRUS STRAINS OF 1930 AND 1931 AND BETWEEN OTHER VIRUSES OF THE FILTER-PASSING GROUP

It has been proved by *in vitro* neutralization experiments on small animals that the virus of 1930 is identical with that responsible for the epidemic of 1931. Furthermore, horses immunized with Virus A (1930) prove also refractory to infection by intracerebral inoculation with Virus B (1931).

Monkeys recovered from experimental poliomyelitis are still susceptible to the virus of encephalomyelitis. No cross neutralization exists between the encephalomyelitis serum and the poliomyelitis virus, and *vice versa*, the poliomyelitis serum lacks antiviral substances for the encephalomyelitis virus (Howitt, 1931).⁶

Guinea pigs and rabbits proven immune to the encephalomyelitis virus by repeated intracerebral inoculations may succumb to an injection by the same route of the virus of Borna disease (obtained through the courtesy of Prof W. Zwick). Reverse cross immunity tests have not furnished conclusive results. Although rabbits and guinea pigs may be immunized against the virus of Borna disease, many months may elapse (on account of the characteristically long incubation time) before the existence of an immunity is

definitely established. As already stated, older guinea pigs, and especially older rabbits, possess a natural immunity to the encephalomyelitis. The apparent refractory state to the encephalomyelitis virus of an older animal, which may be immune to Borna disease, may therefore be merely the expression of a natural immunity and in no way prove the existence of cross protection.

TRANSMISSION OF EQUINE ENCEPHALOMYELITIS TO MAN

Although many important questions concerning the nature of the virus, its pathogenesis and portal of entry into the body of the horse, its epidemic spread, etc., remain unsolved, it appears important to continue the investigations, particularly in view of the recently recognized possibility that man may become the victim of the equine encephalomyelitis virus. Conclusive proof is missing, since the brain tissues of the suspected cases were not tested for the presence of a virus. However, the circumstances, and the clinical and anatomical manifestations are sufficiently suggestive to warrant brief consideration.

Case I. On July 23, 1931, the Woodland Clinic admitted C. G., an American ranch hand, age 43, in a semi-comatose condition, and with a history of fever of four days duration, slight headache in the occipital region, and pain in the neck, thorax and lumbar region. He was restless and disoriented. A week preceding the onset he had attended several horses which had become sick and died from encephalomyelitis.

On the day of admission six days after the onset, the patient complained of dizziness and headache. He was easily aroused from his semi-comatose state but immediately fell to sleep again in no apparent distress. The deep reflexes were sluggish, the Babinski reflex negative, the pupils reacted to light and were normal in size. During the next days

patient became more lethargic. Following a transfusion on July 25, he improved considerably, but succumbed to respiratory failure on July 27, four days after admission. The autopsy revealed no gross anatomical lesions aside from a terminal bronchopneumonia, a moist, markedly injected central nervous system, and a spinal fluid with 200 cells per c.c. (60 per cent polynuclears). An incomplete neuropathological examination demonstrated a slight inflammatory reaction in the meninges, particularly in the depths of the sulci and surrounding the cortical vessels. Focal and diffuse parenchymatous infiltrations with lymphocytes and leucocytes were quite numerous in the cortex, the thalamus and the pons. Dr. G. Y. Rusk, who saw the sections, considers the lesions characteristic of an unusual type of encephalitis resembling the infective encephalitis of the horse.

Case II In October, through the courtesy of Dr. J. M. Wolfsohn of San Francisco and Dr. Frank W. Lee of Sacramento, a report of a case of encephalitis had been received. The patient in question had cared for his horse which suffered from encephalomyelitis late in September. The course of the patient's illness had all the characteristics of an atypical encephalitis which suggested a suspicious connection with that of the horse. During convalescence a sample of the blood

serum was subjected to an *in vitro* neutralization test with equine encephalomyelitis virus with a negative result. Early in January the patient had not entirely recovered.

In view of these observations* a plea is made that the brain and cord of every fatal atypical human case of encephalitis be examined for the presence of the equine virus (by intracerebral inoculation of guinea pigs or monkeys). The latter species is preferred, since larger amounts of the brain suspension may be injected and the course of the disease may be more readily followed by the inexperienced.

In order to keep a record of the many diversified observations, a series of moving pictures has been taken in the field and in the laboratory, during the epidemics of 1930 and 1931. The film supplements the preceding remarks and thus completes a brief survey of the present knowledge of the North American encephalomyelitis of the horse and mule.

*A third case of non-fatal encephalitis contracted through the handling of infected horses was seen in a veterinarian in July, 1932.

REFERENCES

- ¹SHERRID, C., und SPATZ, H. Die Ausbreitung der encephalitischen Reaktion bei der Bornaschen Krankheit der Pferde und deren Beziehungen zur Encephalitis epidemica zur Heine-Medinschen Krankheit und zur Lyssa des Menschen. Eine vergleichend-pathologische Studie, *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1930, cxxiv, 317-382.
- ²NICOLAI, S., and GALLOWAY, I. A. Borna disease and enzootic encephalomyelitis of sheep and cattle, *Med. Research Council* 1928-1929, report No. 121, 7-90.
- ³MEYER, K. F., HAYES, C. M., and HOWITT, B. The control of enzootic encephalomyelitis of horses in San Jose, California, *Proc. Soc. 1931*, lxxiv, 227-228.
- ⁴MEYER, K. F., and HAYES, C. M. The control of enzootic encephalomyelitis of horses in San Jose, California, *Proc. Soc. 1931*, lxxiv, 227-228.
- ⁵Vet. Med. Assoc. Report of the committee on miscellaneous transmissible diseases, *Jr. Am. Vet. Assoc.*, 1932, lxxxv, ns xxxiii, 509-512.
- ⁶HOWITT, B. F. Poliomylitis. I. Production of antiviral serums by inoculation of goats' and sheep's virus of poliomyelitis, *Jr. Infect. Dis.*, 1932, I, 26-46. II. Comparison of intramuscular injection with combined intraspinal and intravenous injection of convalescent serum in treatment for experimental poliomyelitis in monkeys, *Jr. Infect. Dis.*, 1932, I, 47-60.
- ⁷HOWITT, B. F. Cross immunization experiments with poliomyelitis virus and that of encephalomyelitis in horses. *Proc. Soc. Exper. Biol. and Med.*, 1931, xxi, 118-120.

Sensitization to Fungi

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MICRO-ORGANISMS may be divided into four distinct groups, namely, the Schizomycetes or bacteria, the Hyphomycetes or molds, the Blastomycetes or yeasts, and the protozoa. The bacteria, molds, and yeasts belong to the plant kingdom, whereas the protozoa belong to the animal kingdom. Fungi, in addition to molds and yeasts, include rusts, smuts, mushrooms, etc. The molds have been classified into five families, with several hundred genera, and thousands of different species. From the viewpoint of allergy, this is a vast unexplored field, and I have selected for study those varieties which have already been reported by other investigators, and also all the different fungi (molds and yeasts) that could be cultured from patients' skin lesions, sputum and nasal secretions, stools, and environmental dusts (house and mattress).

REVIEW OF LITERATURE

Storm van Leeuwen¹ has a clear claim to priority in the field of asthma due to fungi, as he was the first to call attention to the importance of mold allergens in the causation of this disease.

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He² attributed the climatic type of asthma so prevalent in Holland, to products of the growth of molds, yeasts, or bacteria, which he termed "climate allergens or miasms." Storm van Leeuwen³ usually worked with six different molds, namely, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus niger*, *Mucor*, and *Penicillium*, and by testing his asthmatics intracutaneously with extracts of these molds, found about 50 per cent of them sensitive to mold allergens.⁴ He also found about 20 per cent of his asthma patients sensitive to an allergen formed in grain infected with common mites.

Cadham⁵ reported three examples of asthma due to sensitization to grain rusts.

Hansen,⁶ in Germany, found that 15 per cent of his asthmatic patients gave positive skin reactions to one or more of the following molds: *Aspergillus fumigatus*, *Aspergillus niger*, *Penicillium glaucum*, *Aspergillus glaucus*, and *Aspergillus nidulans*. He was able to reproduce asthmatic attacks in a number of these patients with spores of the reacting molds.

Hopkins, Benham, and Kesten⁷ were the first in the United States to report a case of asthma due to a fungus (*Alternaria*). The patient in addition to being markedly sensitive to *Alternaria*

gave definitely positive skin reactions to several other molds, including *Aspergillus nidulans* cultured from an eczematous lesion on his leg. In this connection it may be stated that some years previously, Niethé,⁸ and Hilgermann⁹ had attributed certain cases of eczema to sensitization to common saprophytic molds which grew on the skin lesions.

Bernton¹⁰ has given an account of one patient with asthma due to a mold—*Aspergillus fumigatus*. Specific treatment was attempted in this case, but was discontinued after the third subcutaneous injection of a 1:5000 extract of *Aspergillus fumigatus*, because of the severe asthma produced by these injections.

Ramirez and Eller¹¹ reported two cases of "contact dermatitis" (dermatitis venenata), and one case of asthma and urticaria, due to sensitization to green *Penicillium*.

Flood¹² has just reported the case of one patient with asthma due to sensitivity to *Mucor plumbeus*. He also states that in a group of 55 patients with chronic asthma, 14 per cent gave positive skin reactions to common dust fungi.

Medical literature contains numerous references to Trichophytin hypersensitivity in persons with deep-seated ringworm infections, and Low,¹³ and Bloch¹⁴ have reviewed the subject in detail. More recently, Jadassohn and Peck¹⁵ showed that this skin hypersensitivity to Trichophytin is also quite constantly present in superficial tinea infections. Sulzberger and Lewis,¹⁶ by means of contact or patch tests with Trichophytin demonstrated that products of fungi are capable of causing an eczematous eruption on a hypersen-

sitive skin. Ramirez¹⁷ has reported a case of hay-fever and asthma which could be traced to Trichophytin sensitization. Sulzberger and Kerr¹⁸ recorded the case of a man with tinea of the hands and feet, who gave immediate, marked, urticarial-wheel reactions to intradermal Trichophytin tests. With this patient's blood serum, they were able to passively transfer the urticarial Trichophytin hypersensitivity to the skin of normal nonsensitive individuals, thus demonstrating the presence in the blood of Prausnitz-Kustner antibodies or specific reagins. Wise and Sulzberger¹⁹ reported the case of a patient with dermatitis, and occasional attacks of urticaria, asthma, and hay-fever, in whom an intradermal test with Trichophytin produced an acute attack of hay-fever and generalized hives, necessitating the administration of epinephrin for relief.

ACKNOWLEDGEMENTS

The numerous fungi used in my work have been obtained from various sources. Quite a number of mold cultures have been sent to me from the Laboratory for Medical Mycology of Columbia University College of Physicians and Surgeons, New York, through the courtesy of Drs. Hopkins and Kesten of the Department of Dermatology, and Dr. Chester W. Emmons, Associate in Mycology. Some of the mold preparations were furnished by Dr. Charles Thom, Principal Mycologist of the U. S. Department of Agriculture. Dr. Storm van Leeuwen of Holland, kindly sent me extracts of six different molds, and also an extract of grain infected with mites. Cultures of a few molds were contributed by Dr. Oscar B. Hunter, Professor of Bacteriology and Pathology at the George Washington University School of Medicine. Dr. Hunter has also rendered me invaluable assistance in carrying on most of the laboratory work referred to in this article, and I gratefully acknowledge his wholehearted cooperation. Dried preparations of

several different strains of yeast were supplied by Standard Brands Incorporated. Mushroom and yeast diagnostic proteins were purchased from the Arlington Chemical Company. Trichophytin (Farbenindustrie) was procured through Metz and Company. Dr. Fred Cadham sent me some uredospores of *Puccinia graminis* (wheat rust).

CULTURE, ISOLATION, AND IDENTIFICATION OF FUNGI

Dusts from various sources, principally house and mattress dusts, were cultured on Czapek's solution agar, dextrose agar, and Sabouraud's medium in pour plates. The plates were then incubated at 37.5° C and at room temperature for from three to seven days. These plates were observed daily during this time for evidence of growth, and the characteristics of all colonies were studied. Daily observations were absolutely essential, because of the profuse growth which sometimes occurs in a relatively short time, making it difficult, if not impossible, to isolate the various molds, yeasts, and bacteria in pure culture, unless subcultures and subsequent plates are made.

As soon as the individual colonies made their appearance, they were fished and subcultured on slants of Czapek's solution agar, 1 per cent dextrose agar, Sabouraud's medium, or such other media as were indicated by the morphology of the colony and the characteristics of the organism. These subcultures were then incubated at 37.5° C and at room temperature until the typical colored hyphae developed, during which time daily observations were made as to the progress and characteristics of the growth. Complete coloration of the aerial hyphae usually developed in from one to seven days, de-

pending to some extent on the character and type of the mold. During this time microscopic preparations were examined, and notations made of the method of development of the stalk, conidiophores, spores, etc., of the molds.

After coloration was complete, final observations were made, macroscopically and microscopically, and in many instances, special fermentation tests and biologic determinations were also made. These findings, together with previous observations were compared with known mold cultures. These observations and comparisons, together with reference to the works of Buchanan,²⁰ Thom,²¹ and Gullhermond and Tanner,²² were sufficient in most instances to identify the mold or yeast in question, but in other instances it was possible to report the mold or yeast only as belonging to a group, and not as a specific entity. Some of the media used, and their ingredients, are as follows:

CZAPEK'S SOLUTION AGAR

Distilled water	1000.0 cc
Sodium nitrate	3.0 Gm
Potassium phosphate (K_2HPO_4)	1.0 Gm
Magnesium sulphate	0.5 Gm
Potassium chloride	0.5 Gm
Ferrous sulphate	0.01 Gm
Sucrose	30.0 Gm
Agar-agar	15.0 Gm

DEXTROSE AGAR (1 PER CENT)

Distilled water	1000 cc
Sodium chloride	5 Gm
Meat extract	5 Gm
Peptone	10 Gm
Dextrose	10 Gm
Agar-agar	15 Gm

SABOURAUD'S MEDIUM

Distilled water	1000 cc
Peptone	10 Gm
Maltose	50 Gm
Agar-agar	15 Gm

MALTOSE BROTH (2 PER CENT)

Distilled water	1000 c c
Peptone	10 Gm
Sodium chloride	5 Gm
Meat extract	5 Gm
Maltose	20 Gm

The above media are especially suitable for the growth of molds and yeasts. In addition to these, other special media peculiarly adaptable to certain types of growth were used, and, of course, the routine media for the growth and differentiation of the various bacteria were also used in the work of cultivation, isolation, and identification.

PREPARATION OF POWDERS AND
FILTRATES FROM MOLDS

The molds from which powders and filtrates were to be made were inoculated into malt extract broth. These cultures were allowed to stand at room temperature for from 25 to 30 days, during which time a definite and specific felt developed on the surface of the medium. After growing for this length of time, the felt and broth mixture was filtered through sterile filter paper, and the broth filtrate was caught in a sterile container. The felt, which remained on the filter paper, was dried in the incubator for 48 hours. It was then transferred to a sterile mortar and ground into a fine powder. This powder was placed in a sterile tube, and labeled. In some instances, when the felt did not dry after a period of 48 hours in the incubator, it was necessary to freeze it with "dry ice" and grind the felt in this condition, after which, drying was more or less successful.

The broth filtrate was again filtered,

this time through the Berkefeld candle. This filtrate was then transferred to a sterile vaccine vial, and cultured for sterility, both aerobically and anaerobically, for at least 72 hours, after which it was kept in the refrigerator until needed.

The medium used for growing molds for this purpose consists of a 10 per cent solution of malt extract in distilled water. This medium seems to be superior to other preparations, for the development of a massive felt and a potent filtrate. The yeasts were cultured in a manner similar to that used for molds and for bacteria. The types of media most suitable for the growth of yeasts, are sugar broths and beer wort, with or without the addition of agar or gelatin.

METHOD OF PREPARING MOLD
EXTRACTS

Concentrated (2 per cent) glycerin extracts of the various fungi have been prepared, in addition to the dried powdered felts, and sterile broth filtrates just referred to. These glycerin extracts were prepared by adding one gram of the dried powdered felt to 50 c c of an extracting fluid, which consists of 50 per cent glycerin and 50 per cent buffered salt solution. Some sterile glass beads were added to facilitate shaking, and prevent clumping. The buffered salt solution was made by adding 27 grams of sodium bicarbonate and 5 grams of sodium chloride to 1000 c c of distilled water. These extracts were kept in the refrigerator for a week, and thoroughly shaken at least once daily. The extracts were then filtered through a Berkefeld candle and examined for sterility.

FUNGI STUDIED

My collection of fungi at the present time is as follows

Alternaria humicola
Alternaria mali
Alternaria sp (five strains)
Aspergillus candidus
Aspergillus clavatus
Aspergillus conicus
Aspergillus flavipes
Aspergillus flavus
Aspergillus fumigatus (nine strains)
Aspergillus glaucus (eleven strains)
Aspergillus hortai
Aspergillus nidulans (eight strains)
Aspergillus niger (seven strains)
Aspergillus ochraceus
Aspergillus oryzae
Aspergillus parasiticus
Aspergillus terreus
Aspergillus versicolor (two strains)
Aspergillus Wentii
Aspergillus sp
Cephalothecium roseum (*Trichothecium roseum*)
Citromyces sp
Cladosporium sp
Dicoccum asperum
Endothia parasitica
Fusarium orthoceras
 Grain smut
Hormodendrum hordei
Monilia albicans (two strains)
Monilia parapsilosis
Monilia sitophila
Monilia sp
Mucor circinelloides
Mucor erectus
Mucor fragilis
Mucor griseocyaneus
Mucor mirus
Mucor mucedo (eight strains)
Mucor piriformis
Mucor plumbeus (three strains)
Mucor racemosus (two strains)
Mucor sp (three strains)
 Mushroom (food)
Neurospora sitophila (ascomycetous stage of *Monilia sitophila*)
Paecilomyces varioti

Penicillium brevicaulis
Penicillium chlorophaeum
Penicillium chrysogenum
Penicillium cyclopium
Penicillium elongatum
Penicillium expansum (seven strains)
Penicillium glaucum (green—nine strains)
Penicillium griseo-roseum
Penicillium italicum (two strains)
Penicillium lanosum
Penicillium oxalicum
Penicillium Pfefferianum
Penicillium sp (two strains)
Polyporus versicolor
Puccinia graminis (uredospores)
Rhizopus nigricans
Saccharomyces cerevisiae (four strains)
Saccharomyces torulae
Saccharomyces sp (three strains)
Sporotrichum Beurmannii
Trichoderma Konigii
Trichophyton gypsum
Trichophyton mixed (gypsum, cerebriforme, migroides, crateriforme, rosaceum, and violaceum)
Ustilago maydis (corn smut)

* TESTING AND TREATING WITH FUNGI

A considerable number of patients with asthma, eczema, hay-fever and other related conditions, have been tested more or less routinely for sensitization to fungi. The cutaneous or "scratch" method has been used almost exclusively, but in a few selected cases resort has been had also to the intradermal method of testing.

The crude molds growing on Sabouraud's or Czapek's media may be used for cutaneous testing, but they are somewhat awkward and messy to handle. The principal objection, however, to the use of crude molds for diagnostic skin tests is that the spores get in the air and contaminate almost every-

thing in the office or clinic where they are being handled

The dried powdered felt makes satisfactory material for the "scratch" test, and is dissolved on the skin with tenth-normal sodium hydroxide solution, just as in tests with other dried protein preparations. The same objection, however, applies to the use of the dried felt for test purposes as to the crude molds, namely, that some of the spores are bound to get into the air, and, if viable, will contaminate almost anything they come in contact with.

The sterile broth filtrates may be used undiluted for cutaneous or intradermal testing, and in proper dilution for treatment purposes. However, as these filtrates consist of nutrient broth without any preservative, they are quite easily contaminated, and must, therefore, be handled with strict aseptic precautions. Sterile normal salt solution was used to prepare 1:10, 1:100, and 1:1,000 dilutions of the broth filtrates for treatment purposes.

The concentrated glycerin extracts previously referred to are potent and stable, and perfectly satisfactory for cutaneous testing, but because of the high content of glycerin, must be diluted at least ten times with sterile buffered salt solution to make them suitable for intradermal testing. In preparing dilutions of the glycerin extracts for treatment purposes, however, the glycco-saline extracting fluid should be used as diluent, to maintain the potency and sterility of these dilutions.

In testing with the various preparations of the fungi, suitable controls should be used, namely, tenth-normal sodium hydroxide for the crude molds and the dried powders, sterile malt ex-

tract broth for the broth filtrates, the glycco-saline extracting fluid for the glycerin extracts, and phenolized salt solution for the *Trichophyton*.

CASE REPORTS

Excerpts from case records of some of my patients will now be given, to illustrate certain phases of the subject under discussion.

Case I Mr. T., aged 37, with chronic asthma, had noticed that his trouble was aggravated by damp, musty places, and rainy weather. The asthma was so constant that it necessitated his taking one or two $\frac{3}{8}$ gram ephedrine capsules from three to six times daily to keep it under control.

Exhaustive skin testing by the cutaneous or "scratch" method showed him to be definitely sensitive to a great many different kinds of molds. In the order of their importance according to the size of the skin reaction, they were *Penicillium glaucum*, *Penicillium mixed*, *Aspergillus nidulans*, *Aspergillus parasiticus*, *Mucor mixed*, *Alternaria mali*, *Aspergillus fumigatus*, *Aspergillus terreus*, *Penicillium cyclosporum*, *Aspergillus glaucus*, *Penicillium expansum*, *Penicillium italicum*, *Aspergillus niger*, *Penicillium lanosum*, *Aspergillus oryzae*, *Citromyces sp.*, *Penicillium chlorophaceum*, *Mucor mucedo*, and *Aspergillus candidus*. Some of these will be recognized as newcomers to be added to the already lengthy list of allergens.

With this patient's blood serum, a single attempt was made to transfer the sensitization to *Penicillium mixed*, *Aspergillus nidulans*, and *Aspergillus parasiticus* to the skin of a normal nonsensitive person. The *Penicillium* mixture gave a positive transfer, but the *Aspergilli* were negative.

Mr. T.'s dominant reaction was to the dried felt from a flask which had been inoculated with two green *Penicillia* (*P. chlorophaceum* and *P. chrysogenum*), and consisted of an irregular urticarial wheal $1\frac{1}{2}$ inches in diameter, surrounded by a zone of erythema, and accompanied by a subjective sensation of itching. The sterile broth filtrate from this

same flask also gave a marked positive reaction. Strange as it may seem, tests with dried felt and broth filtrate from the same culture of *P. chlorophaeum*, and with felt and filtrate from the culture of *P. chrysogenum*, were entirely negative. Retests with subcultures of these two molds were also negative, with the exception of a mild positive reaction to *P. chlorophaeum*. It would seem that these two green *Penicillia* growing together produced some allergenic substance that was not formed by either mold growing alone. Another possible explanation would be that the original flask containing the mixture of the two *Penicillia* had become contaminated with some other mold to which this particular person happened to be highly sensitive. This is quite unlikely, however, when we consider that this patient was carefully tested with my entire collection of mold preparations, without showing any reaction to equal even the one elicited by the dried felt from the green *Penicillium* mixture. Similarly, this individual gave a marked positive reaction to a skin test with the dried felt from a flask which had been inoculated with four different *Penicillia* (*P. elongatum*, two strains of *P. expansum*, and *P. cyclopium*), but tests with preparations of each of these same four *Penicillia* separately, were all completely negative with the exception of a moderate reaction to the dried felt of *P. cyclopium*. Furthermore, this same person gave a definitely positive reaction to the dried felt from a flask which had been inoculated with five different *Mucors* (*M. plumbeus*, *M. griseocyanus*, *M. circinelloides*, *M. mirus*, and *M. mucedo*), but failed to react to preparations of any of these same five *mucors* separately, with the exception of a slight reaction to the dried felt of *M. mucedo*.

These three instances bring up, for the first time, the question of symbiosis in sensitization to fungi. In an effort to further elucidate this problem of symbiotic allergens, three additional flasks have been inoculated respectively with subcultures of the two green *Penicillia*, the four *Penicillia*, and the five *Mucors* just referred to, for the preparation of dried felts and broth filtrates. When these are ready, they will be tested on this same patient to see if they will react similar-

ly to the preparations from the original mixtures.

It is interesting to note that this patient's asthma was definitely aggravated by inhalation of some of the spores, incident to skin testing him with the crude molds and the dried felt preparations. After this happened several times, the precaution was taken of tying a folded handkerchief over his nose and mouth while the dry mold preparations were being handled in his presence.

Cutaneous tests with crude nonsterile extracts of his own house dust, mattress dust, pillow dust, bedroom rug dust, and automobile upholstery dust were all negative. These individual dust specimens were collected with a vacuum cleaner, with paper sacks substituted for the cloth bag of the cleaner, as described by Cohen.²³ In spite of his not reacting to these autogenous dust extracts, it was deemed advisable for him to purchase a new mattress and pillows and have them covered with Dupont's satin fabrikoid, which is impervious to dust and molds. Also, his sleeping quarters were thoroughly cleaned and all unnecessary dust catchers were eliminated. Following these changes, he has been able to discontinue the ephedrine entirely, and although he still has some asthma every day, the attacks now are relatively mild and of short duration. It would be impossible to say how much of this improvement should be attributed to the changes in his sleeping quarters, for he was being given at the same time, an intensive series of injections of concentrated peptone extract, for its nonspecific desensitizing effect. Unless the asthma leaves him entirely in the near future, he will be given a course of hyposensitizing injections with various dilutions of the broth filtrate from the green *Penicillium* mixture previously referred to.

Case II Mr. C. aged 32 was referred to me with severe asthma of eleven years' duration. He had noticed that while staying in certain places he was practically free of asthma for months at a time. His asthma was definitely worse in summer, and better in cold, dry weather. The attacks, which were accompanied by a good deal of coughing, almost always came on indoors and usually occurred either at night or in the fore-

retiring, or early in the morning. He also stated that dust affected him. These points in his history suggested sensitization to molds.

Skin testing by the cutaneous method showed him to be definitely sensitive to extracts of his own mattress and house dusts, the former being slightly more potent than the latter. He also gave definitely positive reactions to "scratch" tests with the dry dusts themselves. That these dust reactions were due to a specific sensitization, and not merely to a nonspecific irritation or histamine reaction, was proven by the fact that these same dusts failed to react when they were tested on the skin of other persons (allergic and nonallergic). Skin tests with epidermals, pollen, orris root, and other air-borne substances failed to show a reaction that would in any way account for the allergenic properties of his house and mattress dusts. His mattress was cotton felt but a test with cottonseed protein was completely negative. Furthermore, "scratch" tests with dust extracts from various other sources, were all negative. It seemed, therefore, that his specific dust sensitization must be due to some fungus which was present in his mattress, and also to a slightly lesser degree in his house dust. However, "scratch" tests with a number of stock mold preparations were completely negative.

When he was tested intradermally with sterile broth filtrates and extracts of various molds, positive reactions were obtained to the following in the order named: *Aspergillus nidulans*, *Aspergillus fumigatus*, *Aspergillus niger*, *Penicillium* mixed (*P. elongatum*, *P. expansum*, and *P. cyclopium*), *Mucor plumbeus*, *Paecilomyces varioti*, and *Cephalothecium roseum*. Some of these reactions were immediate and some delayed. However, as it was necessary to inject these mold preparations intradermally to obtain positive reactions, none of them definitely explained his immediate urticarial reactions to "scratch" tests with his own house and mattress dusts.

His house dust was then cultured, and showed the following: *Aspergillus niger*, *Aspergillus fumigatus*, *Citromyces* sp., *Saccharomyces* sp., *Bacillus megatherium*

(group), *Bacillus subtilis*, *Bacillus mycoides*, *Bacillus roseus*, and a gram-positive coccus. These were isolated in pure culture and tested by the "scratch" method, but none of them reacted.

In view of the possibility that the reactivity of the house dust might be due to some symbiotic allergen, a flask was inoculated with all of the fungi and bacteria cultured from his house dust, and dried felt and sterile broth filtrate were prepared from this mixture. He will be tested with these preparations during his next visit.

Cultures from his sputum showed *Aspergillus fumigatus*, *Streptococcus hemolyticus*, *Streptococcus viridans*, and *Staphylococcus aureus*. His mattress dust was then cultured with the following findings: *Penicillium glaucum*, *Aspergillus glaucus*, *Citromyces* sp., *Penicillium expansum*, *Aspergillus niger*, *Mucor mucedo*, *Staphylococcus citreus*, *Bacillus megatherium* (group), *Bacillus mesentericus*, and *Bacillus* (chromogenic) *flavus*. It will be noted that four out of the six kinds of molds isolated from the mattress dust were different from those found in his house dust. As I have as yet had no opportunity to test him with these molds from his mattress dust, it is perfectly possible that one of them may be the positive reactor. The reacting substance in the dust is not likely to be any of the bacteria found, as bacteria very rarely give immediate skin reactions. I can recall only two instances of immediate urticarial reactions to "scratch" tests with bacterial proteins.

This patient was told to have his home thoroughly cleaned, and then kept as free of dust as possible. He was also advised to purchase a new mattress and pillows, and have them covered with rubber sheeting to make them impervious to dust. Since he has been sleeping on the new mattress, his asthma has been definitely better. It is significant to note that recently when he tried sleeping on an old cot, his asthma was as bad as ever. When he returned to his new bed, the asthma promptly improved again.

Case III Mr G., aged 51, was referred to me with asthma of about sixteen years' standing, which had started with coughing at night. At times he was also troubled in

the morning with hay-fever symptoms, consisting of burning and watering of the eyes, and sneezing, which symptoms were frequently followed by asthma. His asthma was always worse in the summer and fall and he had lost considerable time from work because of severe attacks at that time of the year. He stated that dust affected him and made him sneeze.

Cutaneous tests with pollens, animal epidermals, bacteria, foods, etc., failed to reveal the cause of his asthma. However, "scratch" tests with extracts of his own mattress and bedroom rug dusts gave definite positive reactions. He also reacted in the same way to an extract of dust from the mattress of another patient living in a different section of the country. Mr. G's mattress was cotton felt and the bedroom rug was woolen, but he was completely negative to tests with cottonseed, cotton, and wool proteins. Tests at that time with some of the more important stock mold preparations were completely negative, with the exception of slight or doubtful reactions to *Cephalothecium roseum*, *Penicillium expansum*, and *Penicillium elongatum*.

He was advised to get rid of the musty old rug which had been on his bedroom floor for over fifteen years, and also to vacuum, sun, and air his mattress at frequent intervals. Since the removal of this rug over a year ago, he has been entirely free of asthma.

Cultures of his mattress dust showed *Penicillium chrysogenum*, *Alternaria* sp., *Aspergillus glaucus*, *Aspergillus niger*, *Mucor mucedo*, *Bacillus subtilis*, *Bacillus megatherium* black (subtilis group), *Bacillus megatherium*—brown (subtilis group), *Bacillus mesentericus* (*fuscus panis viscosi*), *Bacillus roseus*, and a gram-negative bacillus. He has never given me the opportunity to test him with these molds isolated from his dust, and *Penicillium chrysogenum*, *Aspergillus glaucus*, and *Mucor mucedo* were not included in his original tests with stock molds, so one of these three varieties of molds could readily be the allergenic offender. I am most suspicious of the *Penicillium*, for the green *Penicillia* are more frequent reactors than either *Aspergillus alaucus* or *Mucor mucedo*.

Case IV Mrs. T, aged 68, was referred to me with asthma of about eighteen years' duration. She stated that dust of any kind affected her.

Skin tests by the "scratch" method, including the most important molds, were all negative. Cultures from her sputum, in addition to the common respiratory micro-organisms, showed *Alternaria* sp. This finding has probably no significance in her case, however, as she gave absolutely no reaction to a "scratch" test with this particular strain of *Alternaria*, and furthermore, intradermal tests with stock *Alternaria* filtrates were completely negative. When tested intradermally with other important molds, however, this patient gave positive delayed reactions to the following: *Aspergillus nidulans*, *Penicillium mixed*, *Aspergillus conicus*, *Paecilomyces varioti*, *Mucor mixed*, and *Cephalothecium roseum*.

Case V Miss S, 14 years of age, was brought to me with bad eczema which she had had ever since she was a baby in arms. The eczema was practically limited to the exposed parts of her body, namely, her face, neck, and arms. Although this trouble was present throughout the year, it was worse in hot weather. She stated that house dust made her sneeze, and irritated her skin. The eczema left her whenever she went to the mountains, but came back promptly upon her return to sea-level.

Cutaneous tests with fungi showed positive reactions to *Saccharomyces cerevisiae* and *Aspergillus fumigatus*, and slight or doubtful reactions to *Monilia mixed*, *Penicillium expansum*, *Aspergillus terreus*, *Trichophyton gypsum*, *Trichophyton mixed*, *Aspergillus nidulans*, *Citromyces* sp., and *Penicillium griseo-roseum*.

Skin tests with crude extracts of her own general house dust, bedroom rug dust, mattress dust, and pillow dust were all negative. Cultures from her skin lesions failed to reveal any fungi.

As she gave a definite positive skin reaction to the protein of yeast (*Saccharomyces cerevisiae*) she was advised to change her diet all light bread because of its yeast content. Following this change she reported an improvement in the eczema. After doing without bread for some time she

retiring, or early in the morning. He also stated that dust affected him. These points in his history suggested sensitization to molds.

Skin testing by the cutaneous method showed him to be definitely sensitive to extracts of his own mattress and house dusts, the former being slightly more potent than the latter. He also gave definitely positive reactions to "scratch" tests with the dry dusts themselves. That these dust reactions were due to a specific sensitization, and not merely to a nonspecific irritation or histamine reaction, was proven by the fact that these same dusts failed to react when they were tested on the skin of other persons (allergic and nonallergic). Skin tests with epidermals, pollen, orris root, and other air-borne substances failed to show a reaction that would in any way account for the allergenic properties of his house and mattress dusts. His mattress was cotton felt but a test with cottonseed protein was completely negative. Furthermore, "scratch" tests with dust extracts from various other sources, were all negative. It seemed, therefore, that his specific dust sensitization must be due to some fungus which was present in his mattress, and also to a slightly lesser degree in his house dust. However, "scratch" tests with a number of stock mold preparations were completely negative.

When he was tested intradermally with sterile broth filtrates and extracts of various molds, positive reactions were obtained to the following in the order named: *Aspergillus nidulans*, *Aspergillus fumigatus*, *Aspergillus niger*, *Penicillium* mixed (*P. elongatum*, *P. expansum*, and *P. cyclopium*), *Mucor plumbeus*, *Paecilomyces varioti*, and *Cephalothecium roseum*. Some of these reactions were immediate and some delayed. However, as it was necessary to inject these mold preparations intradermally to obtain positive reactions, none of them definitely explained his immediate urticarial reactions to "scratch" tests with his own house and mattress dusts.

His house dust was then cultured, and showed the following: *Aspergillus niger*, *Aspergillus fumigatus*, *Citromyces* sp., *Saccharomyces* sp., *Bacillus megatherium*

(group), *Bacillus subtilis*, *Bacillus mycoides*, *Bacillus roseus*, and a gram-positive coccus. These were isolated in pure culture and tested by the "scratch" method, but none of them reacted.

In view of the possibility that the reactivity of the house dust might be due to some symbiotic allergen, a flask was inoculated with all of the fungi and bacteria cultured from his house dust, and dried felt and sterile broth filtrate were prepared from this mixture. He will be tested with these preparations during his next visit.

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This patient was told to have his home thoroughly cleaned, and then kept as free of dust as possible. He was also advised to purchase a new mattress and pillows, and have them covered with rubber sheeting to make them impervious to dust. Since he has been sleeping on the new mattress, his asthma has been definitely better. It is significant to note that recently when he tried sleeping on an old cot, his asthma was as bad as ever. When he returned to his new bed, the asthma promptly improved again.

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the morning with hay-fever symptoms, consisting of burning and watering of the eyes, and sneezing, which symptoms were frequently followed by asthma. His asthma was always worse in the summer and fall and he had lost considerable time from work because of severe attacks at that time of the year. He stated that dust affected him and made him sneeze.

Cutaneous tests with pollens, animal epidermals, bacteria, foods, etc., failed to reveal the cause of his asthma. However, "scratch" tests with extracts of his own mattress and bedroom rug dusts gave definite positive reactions. He also reacted in the same way to an extract of dust from the mattress of another patient living in a different section of the country. Mr. G's mattress was cotton felt and the bedroom rug was woolen, but he was completely negative to tests with cottonseed, cotton, and wool proteins. Tests at that time with some of the more important stock mold preparations were completely negative, with the exception of slight or doubtful reactions to *Cephalothecium roseum*, *Penicillium expansum*, and *Penicillium elongatum*.

He was advised to get rid of the musty old rug which had been on his bedroom floor for over fifteen years, and also to vacuum, sun, and air his mattress at frequent intervals. Since the removal of this rug over a year ago, he has been entirely free of asthma.

Cultures of his mattress dust showed *Penicillium chrysogenum*, *Alternaria* sp., *Aspergillus glaucus*, *Aspergillus niger*, *Mucor mucedo*, *Bacillus subtilis*, *Bacillus megatherium* black (subtilis group), *Bacillus megatherium*—brown (subtilis group), *Bacillus mesentericus* (*fuscus panis viscosi*), *Bacillus roseus*, and a gram-negative bacillus. He has never given me the opportunity to test him with these molds isolated from his dust, and *Penicillium chrysogenum*, *Aspergillus glaucus*, and *Mucor mucedo* were not included in his original tests with stock molds, so one of these three varieties of molds could readily be the allergenic offender. I am most suspicious of the *Penicillium* for the green *Penicillia* are more frequent reactors than either *Aspergillus glaucus* or *Mucor mucedo*.

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Case V Miss S, 14 years of age, was brought to me with bad eczema which she had had ever since she was a baby in arms. The eczema was practically limited to the exposed parts of her body, namely, her face, neck, and arms. Although this trouble was present throughout the year, it was worse in hot weather. She stated that house dust made her sneeze, and irritated her skin. The eczema left her whenever she went to the mountains, but came back promptly upon her return to sea-level.

Cutaneous tests with fungi showed positive reactions to *Saccharomyces cerevisiae* and *Aspergillus fumigatus*, and slight or doubtful reactions to *Monilia mixed*, *Penicillium expansum*, *Aspergillus terreus*, *Trichophyton gypsum*, *Trichophyton mixed*, *Aspergillus nidulans*, *Citromyces* sp., and *Penicillium griseo-roseum*.

Skin tests with crude extracts of her own general house dust, bedroom rug dust, mattress dust, and pillow dust were all negative. Cultures from her skin lesions failed to reveal any fungi.

As she gave a definite positive skin reaction to the protein of yeast (*Saccharomyces cerevisiae*), she was advised to eliminate from her diet all light bread, yeast cakes, etc., of high content. Following this elimination, she reported an improvement in the eczema. After doing without bread for several days, she

eating it again, which apparently caused an aggravation of her skin trouble

Case VI. Mrs F, aged 67, was referred to me in 1926 with severe asthmatic bronchitis, which she had had almost constantly for about nine or ten years. Cultures from her sputum showed, in addition to the common respiratory organisms, a number of colonies of *Aspergillus fumigatus*. A concentrated saline suspension of the spores of this mold was prepared, and tested intradermally on this patient, but with negative results. The failure to obtain a positive reaction may have been due to the fact that heat was used to sterilize the spore suspension, which could have destroyed its allergic reactivity.

Case VII. Miss J, aged 26, was referred to me complaining of bad sneezing spells, irritation of her throat, and recurrent attacks of rather severe pains in her back, shoulders, and limbs. This trouble was usually worse in the summer.

Thorough skin testing by the "scratch" method revealed a marked positive reaction to *Alternaria mali*, and slight or doubtful reactions to *Alternaria humicola* and cheese. *Alternaria mali* is the cause of apple leaf-spot disease, and this patient lives in Winchester, Va., which is the heart of the apple-growing country. It seems highly probable, therefore, that her symptoms, especially the sneezing and irritation of her throat, have been due to inhalation of the spores of this mold. As to the possibility that the recurring attacks of pain in various parts of her body were due to *Alternaria* sensitization, I should like to call attention to the observation of Gehlen and Otto,²⁴ that many of their patients with asthma also had rheumatic symptoms, and that most of them gave positive reactions to cutaneous tests with mold fungi. After testing 125 such patients, most of whom lived in damp houses, they concluded that there was an etiological relationship between asthma and rheumatism, and that sensitization to mold fungi was of some significance in the pathogenesis of these diseases.

Miss J is showing very definite improvement under gradually increasing doses of *Alternaria mali* filtrate. Careful culturing of a single specimen of this patient's house dust

failed to reveal any *Alternaria*, but showed *Mucor piriformis*, *Aspergillus nidulans*, *Mucor racemosus*, *Aspergillus glaucus*, *Aspergillus fumigatus*, *Penicillium glaucum*, *Bacillus subtilis*, and *Bacterium vermiformis*. The failure to find *Alternaria* in her house dust, may have been due to the fact that the dust was collected from a newly built house, into which she had just recently moved.

Case VIII. L, a girl, 11 years of age, was referred to me with asthma of five years' duration. Her trouble was worse at night than in the daytime, and was worse indoors than out. She was better at school than at home, and during several visits away from home was entirely free of asthma.

"Scratch" tests showed an immediate urticarial reaction to dust from her own mattress, and a delayed positive reaction to an unidentified yeast from another patient's house dust. L's mattress was cotton felt, but she gave no reaction whatever to tests with cotton and cottonseed. Culture of a specimen of dust from her mattress showed *Mucor plumbeus*, *Aspergillus glaucus*, *Penicillium expansum*, and *Penicillium glaucum*, but tests with these molds were completely negative. Likewise, tests with my stock molds were all negative.

A flask was then inoculated with the four molds isolated from her mattress dust, and dry powdered felt and sterile broth filtrate were prepared from this mixture. No reactions were obtained, however, when she was tested with these symbiotic mold preparations. As it was believed that something must have been missed, another specimen of dust was collected from the same mattress, and then cultured for fungi, with the following findings: *Saccharomyces* sp., *Aspergillus ochraceus*, *Penicillium brevicaulis*, *Alternaria* sp., *Aspergillus flavipes*, and *Aspergillus oryzae*. "Scratch" tests with these six fungi were all negative, with the exception of very slight or doubtful reactions to the *Alternaria* and *Aspergillus oryzae*. In other words, examination of two separate specimens of dust collected from the same mattress, revealed entirely different fungi, none of which explained this patient's sensitivity to the dust. This shows the multiplicity of molds present in dust, and the difficulty in locating the

offending one by the culture method. From the fact that a small quantity of the dry dust from the mattress, when applied to a "scratch" on the patient's skin and moistened with a drop of tenth-normal sodium hydroxide, gave a definite positive reaction, it may be assumed that the reacting substance was generally distributed throughout the dust. If the reacting substance consists of spores of some fungus, which is the most probable explanation, the failure to find this fungus may be due to the spores being non-viable from age and drying, which would not interfere with their allergenic properties, but would prevent their growth when transferred to culture media.

As *Aspergillus ochraceus*, *Penicillium brevicaulis*, *Aspergillus flavipes*, and *Aspergillus oryzae* isolated from the second specimen of mattress dust, were not included in my collection of stock molds, dry powdered felt and sterile broth filtrate were prepared from each, and she will be tested with these preparations on her next visit. Also, two separate flasks were inoculated with all ten of the fungi isolated from both specimens of the mattress dust, and to one of these flasks was added some sterile cotton fiber and cottonseed meal, to reproduce, as nearly as possible, the conditions within the mattress. Dried felt and broth filtrates have been prepared from each of these flasks. As it was thought that the fungi might have produced the allergenic substance by some action on the cottonseed protein within the mattress, a batch of cottonseed meal was moistened with water and inoculated with all ten fungi isolated from the mattress dust. After this mixture had stood for about a month, being remoistened when necessary to promote free growth of the fungi, the mass was dried, and will be used to test this patient.

When it was discovered that she was sensitive to the dust from her own mattress, instructions were given to get rid of this mattress, and substitute another one, the dust from which did not react on her skin. Since getting rid of the offending mattress, about a year ago, she has remained entirely free from asthma.

Case IX Master D, aged 11 years, was brought to me with asthma, with which he

had suffered since he was about one year old. His trouble was worse in the spring and summer. One particularly severe attack followed a night spent in the cabin of a schooner, and although he was perfectly well when he went to bed, he was so bad by the next day that he had to be carried from the boat. I could not get hold of a specimen of dust from the mattress he used on the boat, but in all probability it was full of mold.

Thorough "scratch" testing gave marked positive reactions to *Alternaria mali*, *Saccharomyces sp.*, *Saccharomyces cerevisiae*, and *Monilia sitophila*, and moderate to mild positive reactions to *Dicoccum asperum*, *Aspergillus nidulans*, grain smut, *Penicillium lanosum*, *Monilia mixed*, *Aspergillus fumigatus*, mushroom (food), *Alternaria humicola*, *Aspergillus clavatus*, *Aspergillus conicus*, *Aspergillus terreus*, *Penicillium cyclophum*, and *Penicillium elongatum*. In spite of his multiple sensitivity to fungi, "scratch" tests with various dust extracts, stock and autogenous, were all negative.

He thought that his asthma was aggravated by contact with cats or dogs, but skin tests with the proteins of cat and dog hair were negative. Some of the molds to which he is sensitive could be present on the hair of cats and dogs, and account for his having symptoms from proximity to these animals, similar to the case reported by Hansen.⁶

With this patient's blood serum, a perfect transfer of the *Alternaria mali* sensitization to the skin of a normal nonsensitive person was obtained. A single unsuccessful attempt was made to passively transfer the *Aspergillus nidulans* and mushroom sensitizations.

It was decided to give him specific treatment for the *Alternaria mali* sensitization, and the desensitizing injections were started with 0.1 cc of a 1:1,000 dilution of a broth filtrate of this mold. The doses have been gradually increased at weekly intervals, and at the present writing he is getting 0.26 cc. of a 1:10 dilution of *Alternaria mali* broth filtrate. There have been no constitutional reactions following any of these doses. Since the institution of this treatment he has been practically free of asthma.

Case X Miss G, 54 years old, was referred to me with chronic asthma. Her first

attack came on just after she had been doing her spring housecleaning

"Scratch" tests showed slight reactions to the following molds *Cephalothecium roseum*, *Aspergillus nidulans*, *Cladosporium* sp, grain smut, *Alternaria mah*, *Puccinia graminis*, *Aspergillus hoitai*, *Trichophyton gypsum*, and *Alternaria* sp. She gave a doubtful reaction to a crude extract of dust from her mattress. The mattress was made of horse hair, but tests with the proteins of horse hair or dander were completely negative. Cultures of dust from this mattress showed *Aspergillus glaucus*, *Mucor mucedo*, *B coli* group, *Bacillus megatherium* (subtilis group), *Bacillus subtilis*, and *Bacillus mesentericus* (*fuscus pans viscosi*), but skin tests with these cultures were all negative. Two separate flasks were inoculated with all of the molds and bacteria isolated from the mattress dust, and some horse hair was also added to one of these flasks. Slight reactions were obtained when she was tested cutaneously with the dried felt from both of these flasks, the mixture with the added horse hair giving a little larger reaction than the other. She was advised to sleep on another mattress, the dust from which gave absolutely no reaction when she was skin tested with it.

This patient was also tested intradermally with concentrated broth filtrates of a number of my stock molds, and gave definite, delayed positive reactions to the following *Cephalothecium roseum*, *Aspergillus nidulans*, *Mucor mixed*, *Penicillium mixed*, and *Penicillium glaucum*. The reaction to *Cephalothecium roseum* stayed inflamed and itched for a week, and the skin desquamated over this area. The reaction to *Aspergillus nidulans* itched for three days.

It was then decided to give her desensitizing injections with the *Cephalothecium roseum* broth filtrate. Treatment was started with 0.05 c.c. of a 1:10 dilution, and the doses are being gradually increased at weekly intervals. Her asthma is better, although she still has some trouble every day.

Case XI Miss M, 14 years of age, was brought to me with eczema, involving the face, neck, and arms, which had troubled her since she was 3 weeks old. Skin tests by the

"scratch" method gave a marked positive reaction to *Aspergillus fumigatus*, and slight or doubtful reactions to *Monilia sitophila*, *Citromyces* sp, and *Monilia* sp. Cultures of scales from her skin lesions were negative for fungi, but culture of her stool showed *Aspergillus glaucus*. I have not yet had an opportunity to test this patient with the particular strain of *Aspergillus glaucus* isolated from her stool.

Case XII Master J, aged 5 years, was brought to me with bronchitis of fifteen months' duration, and asthma which he had had every day for the preceding nine months. His asthmatic attacks were so severe at times, that his parents were afraid he would die in one of them. His only real relief was obtained when they took him west to a much higher altitude, where he was entirely free of asthma.

Skin tests by the "scratch" method, including a few of the more important stock molds, were all negative, except for a positive reaction to an extract of dust from his mattress, and mild positive reactions to horse serum and autogenous sofa, chair, and pillow dust extracts. With reference to the reaction to horse serum, I might state that he had been given diphtheria toxin-antitoxin just prior to the onset of his bronchitis.

They were advised to vacuum, sun, and air his mattress at frequent intervals. The sofa and overstuffed chair were removed from his bedroom, and his pillow was changed. His mother then took him west again for the summer, and since their return some months ago, he has had only one attack of asthma.

Case XIII. Master R, 13 years of age, was brought to me with bad asthma which he had had since he was a tiny baby. He stated that any kind of dust "choked him up."

On cutaneous tests, he gave a mild positive reaction to a crude extract of his own house dust, and a definite positive reaction to short ragweed pollen. Cultures of his house dust showed *Mucor fragilis*, *Mucor erectus*, *Penicillium expansum*, *Penicillium glaucum*, *Mucor mucedo*, *Aspergillus* sp, *Bacillus megatherium* (group), and *Micrococcus flavus* (group). When he was tested with these cultures, however, none of them

reacted Likewise, tests with a number of stock molds were all negative A flask was then inoculated with all of the molds and bacteria isolated from this patient's house dust "Scratch" tests with the dried felt and broth filtrate from this symbiotic mixture were completely negative

In all probability, therefore, Master R's reaction to house dust was due to ragweed pollen contained in the dust As a matter of fact, the specimen of dust had been collected shortly following the ragweed pollinating season As further proof of the correctness of this view, I would state that intensive ragweed treatment has made this boy entirely well of asthma

Case XIV E, a girl of 7 years, was referred to me with a history of bronchial trouble since infancy, and asthma for the preceding two or three years Skin tests showed a definite positive reaction to an extract of her own mattress dust, and slight or doubtful reactions to some foods and a few other substances which did not in any way explain her reaction to the mattress dust Tests with some of my stock molds were completely negative

Cultures of her mattress dust showed *Aspergillus glaucus*, *Penicillium chlorophacum*, *B. coli*, *Bacillus fluorescens*, and *Bacillus pyocyaneus* I have not yet had an opportunity to test E with these cultures, but her mattress was changed, and since then she has had definitely less asthma

Case XV Dr R, 43 years old, was referred to me with chronic bronchitis and asthma Cutaneous tests showed a slight reaction to cheese, and doubtful reactions to *Aspergillus hordei*, *Alternaria mali*, and *Saccharomyces sp* Tests with crude nonsterile extracts of his mattress and pillow dust were completely negative

Intradermal tests gave marked positive reactions to *Cephalothecium roseum*, *Aspergillus nidulans*, *Aspergillus parasiticus*, *Penicillium mixed*, and *Penicillium glaucum*, a moderate reaction to *Aspergillus niger*, and slight or doubtful reactions to *Mucor sp*, *Puccinomyces varioti*, *Aspergillus comicus*, *Alternaria mali*, *Aspergillus flavus*, and *Aspergillus fumigatus* All of these intradermal reactions, with the exception of a doubt-

ful immediate reaction to *Cephalothecium roseum*, were delayed, the interpretation being made the day following the tests The site of the *Cephalothecium roseum* test itched for a couple of days, and the skin desquamated over this area Also, the site of the *Aspergillus niger* test itched for two days These same mold preparations were tested intradermally on a nonallergic individual with completely negative results, proving that they were not nonspecifically irritating to normal skin

Case XVI Mr A, 53 years old, consulted me with chronic abdominal pain of undetermined cause Cutaneous tests with foods, bacteria, some of the more important stock molds, etc., were all completely negative

Culture of his stool showed *Aspergillus fumigatus*, but a "scratch" test with the culture of this mold was entirely negative Intradermal tests with *Aspergillus fumigatus* filtrate and extract gave slight or doubtful reactions Under treatment largely directed to changing this patient's abnormal intestinal flora, he has shown marked improvement, including a gain in weight of between 15 and 20 pounds Recent stool cultures were negative for *Aspergillus fumigatus*

Case XVII Mr L, aged 21 years, was referred to me with chronic bronchorrhea, and hyperhidrosis of hands and feet In addition to the hyperhidrosis, his history and the appearance of his hands and feet were strongly suggestive of tinea

Thorough skin testing by the "scratch" method showed positive reactions to *Cephalothecium roseum*, *Trichophyton mixed*, *Trichophyton gypsum*, *Monilia sp*, and *Saccharomyces cerevisiae* There was no question about his sensitivity to *Cephalothecium roseum*, as he reacted to all of the preparations of this particular fungus, namely crude mold, dried felt, broth filtrate, and glycerin extract It is interesting to note that he gave immediate, urticarial reactions to *Trichophyton mixed* and *Trichophyton gypsum*

Cultures from twenty-four hour specimens of his sputum showed the following fungi: *Monilia sitophila*, *Aspergillus candidus*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus Wentii*, *Penicillium sp*, and *Saccharomyces torulae* The *Monilia sitophila* was

first thought to be *Cephalothecium roseum*, which would have checked up perfectly with his sensitization to *Cephalothecium*. Dr Thom showed me how *Monilia sitophila*, which is the common red bread mold, could be differentiated macroscopically from *Cephalothecium roseum* by their method of growth. *Monilia sitophila* tends to leave the medium and run up the side of the tube or flask containing it, whereas *Cephalothecium roseum* stays on the surface of the medium. Tests with sterile broth filtrates prepared from the *Monilia sitophila* were completely negative. Tests with crude cultures of the *Penicillium sp.* and *Saccharomyces torulae* were also negative.

As *Aspergillus candidus*, *Aspergillus Wentii*, and *Saccharomyces torulae* were not included in this patient's original tests with stock fungi, dried felt and broth filtrate have been prepared on each of these three fungi, and he will be tested with these preparations. Microscopic examination of scales from the skin of his hands was negative for fungi, but scales from his feet showed *Trichophyton interdigitale*.

The bronchorrhea and hyperhidrosis have shown some improvement under desensitizing injections of *Cephalothecium roseum* filtrate, starting with 0.1 cc of a 1:100 dilution. Intensive local treatment has been advised for the epidermophytosis of his feet.

Case XVIII Miss C, aged 38, had had asthma almost constantly for thirty years. She said that dust aggravated her trouble. She also gave a history of chronic constipation, and stated that almost everything she ate seemed to cause gas and bloating.

Cutaneous tests revealed a marked positive reaction to yeast (*Saccharomyces cerevisiae*), mild positive reactions to an extract of her own house dust, and *Mucor plumbeus*, and slight or doubtful reactions to *Penicillium glaucum*, *Penicillium lanosum*, *Alternaria mali*, *Mucor mucedo*, *Mucor circinelloides*, *Aspergillus conicus*, *Monilia sitophila*, *Mucor sp.*, mushroom (food), *Mucor* mixed, *Cephalothecium roseum*, *Penicillium griseo-roseum*, *Penicillium* mixed, *Trichoderma Koningsii*, and an extract of her own bedroom carpet dust. A test with a crude extract of her own mattress dust was negative. Ex-

amination of her stool showed many *Blas-tocystis hominis*, which belongs to the yeast family.

Because of her marked sensitization to yeast, all foods containing this substance were eliminated from her diet, and a sterile 1:50 extract of the protein of *Saccharomyces cerevisiae* was prepared for treatment purposes. Desensitizing injections were started with 0.1 cc of a 1:50,000 dilution. Her most recent dose was 0.21 cc of a 1:50 dilution, but so far there has been little change in her asthma.

Case XIX Master H, aged 8 years, was referred to me with asthma of about 4 years' duration. Although his asthma was worse in the summer, he had it every day all the year around. The trouble was worse at night, and in damp, rainy weather.

"Scratch" tests showed a definite positive reaction to the dust from his own mattress, and slight or doubtful reactions to extracts of specimens of dust from two other mattresses in his home, and to *Monilia sp.* and *Endothia parasitica*. Tests with crude extracts of his bedroom rug dust, dust from a fourth mattress in his home, and his general house dust were negative.

His mattress was made of kapok, but he was not sensitive to this substance. It seemed, therefore, that his sensitivity to the dust from this mattress was probably due to some fungus that had gotten into the mattress. Cultures of a specimen of dust from this mattress showed *Aspergillus versicolor*, *Aspergillus clavatus*, *Mucor sp.*, *Aspergillus Wentii*, *Alternaria sp.*, *Bacillus subtilis* (group), *Bacillus aurantiacus*, *Bacillus megatherium*, *Bacillus mesentericus*, and an unidentified yeast or *Monilia*. Tests with these cultures were all negative, with the exception of *Aspergillus Wentii* which gave a slight or doubtful reaction. As *Aspergillus clavatus* and *A. Wentii* had not been included in this patient's original tests with stock molds, dried felt and broth filtrate were prepared from each of these *Aspergilli*, but tests with these preparations were negative. Also, tests were negative with the dried felt and broth filtrate from a symbiotic flask, which had been inoculated with all of the fungi and bacteria isolated from his mattress dust.

Another flask was inoculated with all of the fungi and bacteria from the mattress, and to this flask were also added some sterile kapok fiber and kapok-seed meal, to duplicate, as nearly as possible, conditions within his mattress. To insure sterility of the kapok fiber and seed meal, the fiber was obtained from a freshly opened kapok pod, and the meal was prepared by grinding dry kapok seeds after they were washed a number of times with ether. Master H was tested with the dried felt and broth filtrate prepared from this kapok treated symbiotic flask, with completely negative results. In addition to this, some moistened kapok-seed meal was inoculated with all of the fungi and bacteria cultured from his mattress dust, with the idea in mind that the micro-organisms might act on the kapok-seed protein to produce the allergenic substance present in the mattress dust. This mixture was allowed to stand for about a month, being remoistened when necessary, to favor free growth of the fungi. Then the mixture was dried, and tested on this patient, but gave absolutely no reaction. The reacting substance in his mattress dust is still an unknown quantity.

When it was discovered that he was sensitive to the dust from his mattress, this mattress was disposed of, and since then there has been a marked improvement in his asthma, and a gain in weight of 10 pounds.

Case XX Master B, 6 years of age, was referred to me with asthma. His first attack had followed a visit to Endless Caverns, which is a damp, moldy place. Last summer was spent at the seashore, and his asthma was much worse there than at home. In addition to the asthma, he sneezed and blew his nose most of the time.

Skin tests showed a positive reaction to *Alternaria mali*, and slight reactions to his own house dust and to dust obtained from the house at the seashore, the dust from the seashore house giving a little larger reaction than that from his own home. Tests with crude extracts of specimens of dust from his own mattress, pillows, day-bed, and upholstered chair were negative. Cultures from his own house dust showed *Alternaria* sp and *Aspergillus fumigatus* as the predominating fungi, and also *Aspergillus glaucus*, *As-*

pergillus nidulans, *Aspergillus Wentii*, *Mucor* sp, *Penicillium expansum*, and *Penicillium italicum*. Tests with these cultures were all negative, with the exception of a positive reaction to the *Alternaria*. Cultures of dust from the seashore house revealed *Alternaria humicola* and *Aspergillus glaucus* as the predominating fungi, and also *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus versicolor*, *Mucor mucedo*, *Mucor racemosus*, and *Penicillium expansum*. Tests with these cultures from the seashore house dust were all negative, with the exception of a definite positive reaction to the *Alternaria humicola*, and a slight or doubtful reaction to the *Mucor racemosus*.

As it seemed quite evident that his asthma was due to *Alternaria* sensitization, specific treatment was decided upon. The desensitizing injections were started with 0.1 cc of a 1:1,000 dilution of a broth filtrate of *Alternaria mali*. The doses have been gradually increased at weekly intervals, his most recent dose being 0.64 cc of a 1:100 dilution. Since the institution of this treatment, he has been almost entirely free of asthma. It is interesting to note, that after being free of asthma for some time, his parents took him for a week-end visit to the same house at the seashore. The first night he was there he started to sneeze, and the second night he developed asthma. This trouble left him when he returned home.

Case XXI Mrs. D, 52 years old, was referred to me with status asthmaticus. She had suffered from asthma constantly every day for the preceding twenty-six years. When she first came to me she was taking from ten to twelve hypodermics of morphine every twenty-four hours. She took $\frac{1}{4}$ grain at a dose, and a prescription for one hundred of these tablets would last her only eight to ten days. She also took hypodermics of adrenalin at intervals of thirty minutes to three hours. Damp weather aggravated her asthma, and dust also bothered her.

"Scratch" tests were all negative, with the exception of a doubtful immediate reaction to *Penicillium griseo-roseum*, and a slight or doubtful delayed reaction to *Monilia* sp. Cultures from her sputum revealed *Penicillium glaucum*, and from her stool *Asper-*

gillus niger, but neither of these molds reacted when she was tested with them

Intradermal tests showed slight or doubtful immediate reactions to *Penicillium* mixed and *Paecilomyces varioti*, and definitely positive delayed reactions to *Aspergillus nidulans* and *Paecilomyces varioti*, the former being a little larger than the latter. The site of the *Aspergillus nidulans* test itched a lot for twenty-four hours, which is a good diagnostic sign

Aspergillus nidulans, therefore, was selected for treatment, her first dose consisting of 0.1 cc of a 1:10 dilution of a broth filtrate of this mold. The doses are being gradually increased at weekly intervals. Although this patient is still having some asthma, she shows marked improvement, she has stopped the morphine entirely, and requires only an occasional hypodermic of adrenalin

Case XXII Mr P, 51 years old, was referred to me with facial eczema of about two years' duration. This trouble seemed to be worse in the summer. Cutaneous tests showed slight or doubtful reactions to the following fungi: *Monilia* sp (found in his stool), *Penicillium glaucum*, *Paecilomyces varioti*, *Mucor* mixed, *Alternaria mali*, and *Aspergillus glaucus*. Cultures from his skin lesions were negative for fungi. Under treatment largely directed to changing his abnormal intestinal flora, the skin trouble cleared up

Case XXIII Mrs H, was referred to me with perennial hay-fever, and recurrent eczema of her face, neck, and arms. She was worse in damp, foggy weather, and dust bothered her. Skin tests by the "scratch" method showed slight or doubtful reactions to cheese, and an *Aspergillus glaucus* was cultured from her sputum. A patch or contact test with this culture was negative. Skin tests with crude extracts of her own house and cellar dusts were negative. Cultures of the scales from her skin lesions revealed *Aspergillus glaucus*, *Mucor mucedo*, *Penicillium italicum*, *Sarcina*, and *Streptothrix*, but "scratch" tests with these cultures were all negative. If this patient cooperates sufficiently, patch tests will be done with the

three molds isolated from her skin cultures, and she will also be tested intradermally

Case XXIV Miss B, aged 42 years, was referred to me with chronic asthma. She was also troubled with gas and bloating most of the time. "Scratch" tests showed a marked positive reaction to *Saccharomyces cerevisiae* (yeast), and slight or doubtful reactions to grain smut, *Aspergillus glaucus*, and *Penicillium chrysogenum*. All foods containing yeast were eliminated from her diet, and the bloating promptly disappeared. Furthermore, she has had very little asthma since

COMMENT

Dr Thom has wisely said that "the *Penicillia*, the *Aspergilli*, and the *Mucors* are the weeds of the culture room". I would add that molds are the weeds of the home. Every specimen of house or mattress dust that has been cultured, was found to contain various fungi. The potentiality of molds being air-borne, may be appreciated if we compare the size of the ubiquitous spores with the size of pollen grains. The average diameter of mold spores is from 3 to 5 microns, whereas the diameter of the common air-borne pollen grains is from 15 to 40 microns

SUMMARY

This paper gives the results of an intensive study of sensitization to fungi, including a review of the literature, and the report of twenty-four illustrative cases

Sensitization to fungi must take its place along with sensitization to pollens, animal epidermals, foods, and bacteria in the causation of asthma, eczema, and other related allergic conditions

The method of diagnosing and treating hypersensitiveness to molds and yeasts is essentially the same as that used for other types of allergenic substances

REFERENCES

- ¹STORM VAN LEEUWEN, W Bronchial asthma in relation to climate, Proc Roy Soc Med (Sec Therap and Pharmacol) 1924, xvii, 19-26
- ²STORM VAN LEEUWEN, W Allergic diseases diagnosis and treatment of bronchial asthma, hay-fever and other allergic diseases, 1925, J B Lippincott Company, Philadelphia
- ³Personal communication to the writer from DR. W STORM VAN LEEUWEN.
- ⁴STORM VAN LEEUWEN, W Asthma and tuberculosis in relation to "climate allergens", Brit Med Jr, 1927, ii, 344-347
- ⁵CADHAM, F T Asthma due to grain rusts, Jr Am Med Assoc, 1924, lxxviii, 27
- ⁶HANSEN, K Über Schimmelpilz-Asthma, Verhandl d deutsch Gesellsch f inn Med, 1928, xi, 204-206
- ⁷HOPKINS, J G, BENHAM, R W, and KESTEN, B M Asthma due to a fungus—*Alternaria*, Jr Am Med Assoc, 1930, xciv, 6-10
- HOPKINS, J G, KESTEN, B M, and BENHAM, R W Sensitization to saprophytic fungi in a case of eczema, Proc Soc Exper Biol & Med, 1930, xlvii, 342-344
- ⁸NIETHE, U Die Bedeutung der Gewöhnlichen Schimmelpilze für die menschliche Haut, Arch f Dermat u Syph, 1926, cli, 358-364
- ⁹HILGERMANN, R Die Therapie und Aetologie der chronischen Hautezeme, Munch Med Wchnschr, 1921, lxxviii, 702-704
- ¹⁰BERTON, H S Asthma due to a mold, *Aspergillus fumigatus*, Jr Am Med Assoc, 1930, xcvi, 189-191
- ¹¹RAMIREZ, M A, and ELLER, J J The "patch" test in "contact dermatitis" (dermatitis venenata), Jr Allergy, 1930, i, 489-495
- RAMIREZ, M A, and ELLER, J J Intradermal, scratch, indirect and contact tests in dermatology, Jr Am Med Assoc, 1930, xcvi, 1080-1083
- ¹²FOOD, C A Observations on sensitivity to dust fungi in patients with asthma, Jr Am Med Assoc, 1931, xcvi, 2094-2096
- ¹³LOW, R C Anaphylaxis and sensitization, 1925, William Wood & Company, New York, p 103
- ¹⁴BLOCH, B Allgemeine und experimentelle Biologie der Dermatomykosen, III Die Trichophyten Allergie, Handb d Haut- u Geschlechtskr, 1928, xi, 336
- ¹⁵JADASSOHN, W, and PECK, S M Epidermophytide der Hände, Arch f Dermat u Syph, 1929, clviii, 16-27
- ¹⁶SULZBERGER, M B, and LEWIS, G M Trichophyten hypersensitiveness demonstrated by contact tests, preliminary report, Arch Dermat and Syph, 1930, xxii, 410-413
- ¹⁷RAMIREZ, M A Trichophyten sensitization, case report, Med Jr and Rec 1930, cxxxii, 382
- ¹⁸SULZBERGER, M B, and KERR, P S Trichophyten hypersensitiveness of urticarial type, with circulating antibodies and passive transference, Jr Allergy, 1930, ii, 11-16
- ¹⁹WISE, F, and SULZBERGER, M B Urticaria and hay-fever due to trichophyten (epidermophyton interdigitale), Jr Am Med Assoc, 1930, xcvi, 1504
- ²⁰BUCHANAN, E D, and BUCHANAN, R E Bacteriology, 1930, The Macmillan Company, New York
- ²¹THOM, C, and CHURCH, M B The aspergilli, 1926, Williams & Wilkins Company, Baltimore
- THOM, C The penicillia, 1930, Williams & Wilkins Company, Baltimore
- ²²GUILLEMOND, A, and TANNER, F W The yeasts, 1920, John Wiley & Sons, New York
- ²³COHEN, M B Asthma due to household articles, report of 19 cases due to dusts from mattresses, Jr Lab and Clin Med, 1929, vii, 837-838
- ²⁴GLIHF, H, and OTTO, J Über kongruente Allergie-erscheinungen bei Bronchialerkrankungen und Rheumatismus Deutsch med Wchnschr, 1929 ix, 1964-1966
- GLIHF, H, and OTTO, J Simultaneous occurrence of bronchial and rheumatic diseases, significance of allergic factors in both diseases, Abstr Jr Am Med Assoc 1930 xcvi, 371

Ten Years at the Lymanhurst School for Tuberculous Children

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NUMEROUS cross section studies of tuberculosis have been made In this paper is reported the first ten years of a longitudinal study undertaken at the Lymanhurst School for Tuberculous Children The chief value of the work at Lymanhurst has been in the opportunity to follow the cases over periods of years, and in so doing to write the history of their tuberculous lesions The medical staff engaged in this work is confident that the true story of tuberculosis in the human body has never been told and that it will not be told until this group or some other group of children is followed through the various decades of life; until death from some cause overtakes every one of them Many decades of work are to follow before ultimate conclusions can be drawn However, in ten years we have seen some developments of which we could never have been convinced except by

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actual observation, inasmuch as they have been quite contrary to our former teachings

THE TUBERCULIN TEST

Each year our confidence in the tuberculin test has increased We have come to look upon it as the most specific test in the field of medicine While it is not infallible, we are of the opinion that when properly administered, it fails very rarely Of course, much depends upon the administration of tuberculin The epidermal test of Pirquet was in quite general use over a long period of time, but a number of workers, such as Smith and Hart, have called attention to the greater accuracy of the intracutaneous test of Mantoux In any work we undertake, accuracy is of prime importance, hence we are of the opinion that in tuberculin testing the intracutaneous test is the best and, therefore, should be generally employed Moreover, there is a great advantage in making the Mantoux the standard tuberculin test

At Lymanhurst we now administer 01 mgm of tuberculin as the first dose, and to all who react negatively, we repeat the test using a full milligram. Aronson has very carefully worked out this dosage and finds that in the most hypersensitive individuals no necrosis

or slough will follow the first dose. In none who reacts negatively to this dose will there be necrosis when a full milligram is administered.

When the child reacts positively to the tuberculin test, we are convinced that somewhere in his body there is tuberculosis and that from the development of this, in whatever stage it happens to be, hypersensitiveness to tuberculin or allergy has resulted. Therefore, the test is one for allergy and, so far as we know, not a test for immunity.

THE X-RAY

As soon as a tuberculin test is found to be positive, we seek the location of the focus of tuberculosis. In the body of the child, our best method of finding these foci is by the x-ray film examination, but even this is woefully lacking. By x-ray examination we located questionable to definite foci in 22.91 per cent of the positive tuberculin reactors. This is not surprising when one considers the nature of the

tuberculous focus, the numerous places in the body where it may occur, and the limitations of the x-ray as we now know it. Many tuberculous foci which cause positive tuberculin reactions are microscopic in size. Therefore, they are not detected by the x-ray. Some of them never become large enough to cast visible x-ray shadows. Others may grow to such size that they are easily detected.

Of the total number of children examined in the Out-patient Department at Lymanhurst School, 4,031 were negative to the tuberculin test. Unfortunately, in the early days of our work only the Pirquet test was used. Of this entire number, 90 (2.22 per cent) (table I) showed evidence of pleurisy. In only 2 was effusion definitely found and in another case there was a questionable small effusion. However, in 17 cases there was some thickening of the pleura over an entire lung, suggesting previous pleural effusions.

Of the total number of children examined in the Out-patient Department

TABLE I
Pleural Changes

	NUMBER	PER CENT
From 4,031 Negative Tuberculin Reactors		
Thickening of interlobar pleura	30	74
Diaphragmatic basal pleurisy	40	99
Thickening of pleura over entire lung	17	42
Pleurisy with effusion	2	05
Mediastinal empyema or effusion with thickened pleura	1	02
Total	90	2.22
From 4,737 Positive Tuberculin Reactors		
Thickening of interlobar pleura	59	1.25
Diaphragmatic and basal pleurisy	62	1.31
Thickened pleura over entire lung	33	7
Pleurisy with effusion	12	25
Rib resection	4	08
Total	170	3.50

at Lymanhurst School, 4,737 were positive to the tuberculin test Of this entire number 170 (3 59 per cent) (table I) showed evidence of pleurisy In 12 of these cases there was definite evidence of effusion In 4 cases rib resections had been done, and in 33 cases there was evidence of thickening of the pleura over an entire lung suggesting previous pleural effusions

Since our knowledge of the significance of the x-ray shadows in the hilum region is still incomplete, the roentgenologist must of necessity frequently make a diagnosis of questionable calcification Therefore, with such interpretations one must be extremely careful in following these cases over months or even years to determine whether calcium really is being deposited Among our negative tuberculin reactors, 44 (1 09 per cent) had questionable evidence of calcium in the hilum In 40 cases (99 per cent) there was evidence of slight and moderate

amounts of calcium in the lung hilum (table II) Evidence of Ghon tubercle formation was observed in 24 cases (60 per cent) In one case there were shadows interpreted as calcified nodes throughout both lungs We formerly looked upon such cases as healed miliary tuberculosis However, since Meriwether and Sayers have called attention to the possibilities of certain fungi, particularly aspergillus, resulting in such shadows, we are not certain of the etiology in this case

Among our 4,737 positive tuberculin reactors, 195 (4 12 per cent) (table II) were found to have questionable evidence of calcium in the lung hilum In 443 cases (9 35 per cent) there was evidence of slight, moderate and marked amounts of calcium in the lung hilum Ghon tubercle formation was observed in 286 cases (6 04 per cent) In 38 cases there was questionable evidence of Ghon tubercle formation Calcium in the lung hilum with

TABLE II
Questionable to Definite Childhood Type Tuberculosis

	NUMBER	PER CENT
From 4,031 Negative Tuberculin Reactors		
Questionable calcification in hilum	44	1 09
Slight and moderate calcification in hilum	40	99
Ghon tubercles	24	60
Calcified nodules throughout both lungs	1	02
Marked enlargement of hilum without calcium	4	09
Total	113	2 79
From 4,737 Positive Tuberculin Reactors		
Questionable calcification in hilum	195	4 12
Slight, moderate and marked calcification in hilum	443	9 35
Ghon tubercles	286	6 04
Questionable Ghon tubercles	38	8
Calcification hilum, fibrosis extending into lung parenchyma	26	55
Childhood type tuberculosis in lung parenchyma (inflammatory stage)	41	87
Marked enlargement hilum without calcification	18	38
Marked enlargement hilum-infiltration extending to parenchyma	38	8
Total	1,085	22 91

an area of fibrosis extending into the lung parenchyma was seen in 26 cases, while the childhood type of tuberculosis in the inflammatory stage, involving the lung parenchyma, was seen in 41 cases. In 18 of our patients there was marked enlargement of the hilum region without evidence of calcium. In another group of 38, such marked enlargement of the hilum region was seen without evidence of calcium, but there was parenchymal infiltration extending outward from the hilum into the lung parenchyma.

Thus among 4,031 children reacting negatively to the tuberculin test, only 113 (2.79 per cent) showed any evidence of the childhood type of tuberculosis and 44 (1.09 per cent) of this group had only questionable evidence, while among 4,737 cases reacting positively to the tuberculin test 1,085 (22.91 per cent) showed some evidence of

the childhood type of tuberculosis, although in 195 (4.12 per cent) of these cases the evidence was questionable.

Of the 4,031 children who reacted negatively to tuberculin, 2 cases (0.5 per cent) (table III) had far advanced pulmonary tuberculosis. The negative reaction in these two cases was obtained from the Pirquet test, since the administration of the Mantoux test had not been instituted at that time. Among the negative reactors were no cases of minimal or moderately advanced adult type of pulmonary tuberculosis. Among the 4,737 children who reacted positively to the tuberculin test the adult type of tuberculosis was found in 61 (1.28 per cent) (table III). Of this number the disease was minimal in extent in 24 (50 per cent), 17 of whom also had evidence of the childhood type. Moderately advanced disease was seen in 17 cases (36 per

TABLE III
Adult Type Pulmonary Tuberculosis

	NUMBER	PFR CENT
From 4,031 Negative Tuberculin Reactors		
Far Advanced	2	0.5
From 4,737 Positive Tuberculin Reactors		
Minimal (17 also had demonstrable childhood type)	24	5
Moderately advanced (11 also had demonstrable childhood type)	17	36
Far advanced (9 also had demonstrable childhood type)	20	42
Total	61	1.28
Tuberculosis of Bones and Joints		
From 4,031 Negative Tuberculin Reactors		
Bones and joints	None	
From 4,737 Positive Tuberculin Reactors		
Spine (6 with chest findings)	8	17
Hip joint (5 with chest findings, 1 with no chest examination)	12	25
Knee joint	3	0.6
Shoulder joint and ankle joint	1	0.2
Bones of hand (no chest examination)	1	0.2
Total	25	52

cent), 11 of whom also had evidence of the childhood type of the disease, while far advanced pulmonary tuberculosis was seen in 20 cases (42 per cent (table III), 9 of whom had evidence of the childhood type. It is interesting to note that there was coexisting childhood type of disease in 37 (60.65 per cent) of the cases with the adult type of tuberculosis.

Among 4,031 children reacting negatively to the tuberculin test, not one was found who had evidence of tuberculosis of the bones and joints. Among 4,737 children reacting positively to the tuberculin test, 25 (52 per cent) (table III) were found to have bone and joint involvement. Tuberculosis of the spine was seen in 8 cases, 3 of whom had evidence of childhood tuberculosis in the chest. Two others had pleural involvement and a third had an area of fibrosis extending outward from the hilum into the lung parenchyma. Thus 6 out of the 8 had demonstrable findings in the chest. In 12 cases there was tuberculosis of the hip joint. In 5 of these cases, there was evidence of childhood tuberculosis, one of whom also had moderately advanced adult type tuberculosis. In 3 cases there was tuberculosis of the knee joint, 2 of whom had evidence of childhood tuberculosis in the chest. In one case of tuberculous dactylitis no x-ray film of the chest was made.

Other abnormal conditions were found such as bronchiectasis, pulmonary abscess and pneumonia, which might justify making x-ray films routinely regardless of the tuberculin reaction. However, the number of lesions proved to be due to tuberculosis was quite small in our group, so small in

fact that we now feel it is a reasonably safe procedure to apply the tuberculin test, and make x-ray films only of those who react positively, except in those cases where there is some other special reason for x-ray films.

THE IMPORTANCE OF PROTECTION FROM ADDED INFECTION IN JUVENILE TUBERCULOSIS

If one observes a group of children who are negative to tuberculin over a considerable period of time, some of them if exposed, will become positive reactors. The work of Sir Robert Philip is an outstanding example of this procedure. Moreover, if one applies the Pirquet test or a small dose of tuberculin by the intracutaneous method and repeats the test with a full milligram of tuberculin by the intracutaneous method, one will find some positive to a milligram of tuberculin who were negative to the smaller dose. We have observed the tuberculin test change from negative to positive in 189 cases. There has been a great deal of discussion about whether a tuberculin test once positive ever becomes negative. We have seen the reaction change from positive to negative in 68 cases.

When we began our work at the Lymanhurst School, we were firmly convinced by reason of our previous teaching that the infant is unusually susceptible to tuberculosis and that he has almost no tolerance to tubercle bacilli. We were so convinced that our teachings had been based upon well-established facts that we rendered immediate grave prognoses in every case two years old or under who had evidence of parenchymal disease. We also rendered immediate grave prognoses

when a positive tuberculin reaction was found in the absence of demonstrable chest lesions in this age period. As time passed, we were chagrined to find that our prognoses were nearly always wrong. Most of the infants with parenchymal pathology did not even manifest symptoms of disease and practically none of those with positive tuberculin reactions ever fell ill. This led us to investigate more carefully the literature and determine upon what the previous teachings had been based. The majority of the reports in the literature were from groups of children in hospitals who were definitely ill from tuberculosis and who in reality were suffering from the adult type of disease, which is destructive in children. In the earlier literature, no one had studied over a period of years a group of symptom-free children either from the homes where there was much exposure or where there was no exposure, nor had anyone made serial x-ray films of the chests of such children. Krause made a careful study of the resistance of young and old guinea pigs from which he arrived at the following conclusions:

"1 When young and old guinea pigs are infected intracutaneously with relatively small quantities of virulent tubercle bacilli that are equal for all the animals there is an earlier appearance and more vigorous development of tubercle at the site of inoculation and in the regional lymph nodes in the old animals.

"2 After infection of this nature and heavy enough to cause generalized tuberculosis in the old animals, both young and old guinea pigs developed essentially the same grade of infection. There was nothing to indicate that the young were more susceptible than the old.

"3 When infected subcutaneously with

large quantities of virulent tubercle bacilli in equal dosage, a more extensive and progressive involvement resulted in the young than in the old.

"4 Since under these circumstances the young received per body weight double the quantity of tubercle bacilli that was in itself sufficient to cause progressive and fatal tuberculosis in the old, it is likely that the more advanced infection of the young was the result of overdosage."

Therefore, it would appear to be largely a matter of dosage rather than a matter of susceptibility to tubercle bacilli. Krause, from his wide experience with tuberculosis in man, together with his experimental work, makes the following statement:

"All in all, it is difficult to comprehend the logic of the frequently expressed warning that makes a sharp distinction between children and adults in respect to the dangers of exposure to tuberculous infection. It certainly is by no means clear that, person for person, the child is less resistant than the adult. As it works out in life, it is beyond dispute that the ravages of tuberculosis are in every way greater in later life than in childhood, and, even allowing for differences of environmental factors that determine illness, we would consider the proposition of a higher adult resistance as unproved. There are elements of resistance that would seem to be stronger in the child, there are other elements that appear more effective in the adult. Where the balance lies we do not know, nor may we assume to state. Quite likely it is an individual affair, and attempts to generalize promise to lead us into error.

"It would seem the better wisdom to presume not at all upon a resistance, and required immunity, that must be of undeterminable and hypothetical integrity in any particular case. We shall be following the larger science and come to a safer practical result if we adjudge children and adults alike before the hazards of tuberculous infection. The only rational attitude is to protect all human beings, of whatever age, against exposure. To allow the impression to get

abroad that adults walk within a charmed circle of acquired immunity, that maturity is a privileged age, can lead only to evil, if it is accepted and acted upon. Besides, there is much evidence that it may be far from the truth."

Myers and Kernkamp, working with Lymanhurst children who reacted positively to the tuberculin test at the age of two years or under, found that when they had traced 172 of these children, only 6 had died of tuberculosis. The majority of their group infected in infancy were apparently well at the time they were traced. These observations, together with the findings of others, led us to believe that our former teachings were wrong and that we must recognize the fact that the infant tolerates tubercle bacilli well, except in those cases where reinfection occurs frequently and in which the adult type of tuberculosis develops after allergy has been established. Many such cases die from generalized tuberculosis, including tuberculous meningitis. Therefore, the best treatment for any infant found to react positively to the tuberculin test is the prevention of subsequent exposure to tubercle bacilli. When this has been done, if the exposure has not already gone too far, the prognosis is excellent with practically no treatment or care beyond that which any normal child should receive. Because of this fact, which we feel is now well established, we are firmly convinced that the foster home free from tuberculosis is far better for the child in whose home open tuberculosis exists than the institution. The work of Bernard and others bears witness to the efficacy of this kind of treatment.

DOES FIRST INFECTION PROTECT?

Does first infection with tubercle bacilli protect against subsequent infection? This involves the subjects of immunity and allergy in tuberculosis, concerning which volumes have been written. In reading the literature, one gains the impression that a first infection is the best safeguard that we have against the destructive form of tuberculosis. Much is said about immunity, yet in all of our armamentarium, we have no definite test for immunity. The literature on this subject leaves one with many questions concerning which no answer can be found except those based on personal opinion. The fact that ten thousand children or adults react positively to the tuberculin test, and not one at that particular moment is ill from tuberculosis or has manifestations of tuberculosis in any of its clinical forms, is no safe criterion of immunity to the clinical forms of tuberculosis. In other words, it is only through subsequent observations, over not only years but decades, that one determines whether these ten thousand individuals were actually immunized. In observing children with positive tuberculin reactions through the first ten years of Lymanhurst's existence, our staff members have again been mistaken in the prognoses they render those beyond the period of infancy. We had been taught that if a child is infected after the period of infancy the prognosis is excellent and that the positive tuberculin reaction is an indication that he was well immunized against tuberculosis. When we saw evidence of lime deposits in the form of Ghon tubercles in the lung parenchyma or in the lymph

nodes in the region of the lung hilum and tracheo-bronchial lymph nodes, we rendered splendid prognoses because of the positive tuberculin reaction which to us, then, denoted immunity, and the child's ability to deposit lime which to us, then, denoted healing and vaccination against tuberculosis. When some of these children reached the 'teen ages and we saw developing in their lungs the adult and destructive type of disease, sometimes leading to death rather quickly in spite of everything that we knew by way of treatment, we began to investigate further the evidence upon which the statement concerning immunity to tuberculosis had been based. We could find nowhere in the literature that anyone had observed the same group of children throughout the various decades of life. Therefore, we

were at a loss to know how anyone had a right to the generalizations on this subject which were extant in the literature.

CASE REPORTS

The citation of five of the numerous cases which we have seen at Lymanhurst will illustrate this point. The very first child who entered the Lymanhurst School is such a case. On May 31, 1921, this boy was present at our dedication ceremony. There was clinical tuberculosis in his family. He was positive to the tuberculin test. He was rather thin and pale but he was suffering from a congenital disease which we believed accounted in part, at least, for his appearance. X-ray examination of his chest showed unmistakable evidence of lime deposits in the right lung hilum (figure 1). After a time he was discharged from the Lymanhurst School well immunized and vaccinated, as we thought. Approximately 10 years from the time he was admitted to the School, and when he was 22 years old, he walked into a



FIG 1 From an X-ray film taken November 21, 1922, of the chest of a boy of 12 years. Intimate contact exposure. Tuberculin test positive. Large calcium deposits in the region of the right lung hilum representing childhood type of tuberculosis. Same findings were shown on films made in 1921.

free chest clinic at the Minneapolis General Hospital and the examination revealed extensive pulmonary tuberculosis involving much of the left lung and a small portion of the right lung (figure 2). This was of the adult type and proved to be rapidly progressive. Neither the positive tuberculin reaction, nor the so-called vaccination scar, represented by calcium deposits in the right hilum, prevented the development of destructive tuberculosis or allayed the progress of his disease. Within a few weeks he was dead of tuberculosis. Thus our first Lymanhurst case, about whom we had talked and written so much and for whom we had rendered such an excellent prognosis based upon opinion not fact, shattered our teachings.

On October 27, 1925, a boy of 14 years was brought to the Lymanhurst Out-patient department for examination because of some cough and slight weight loss. There was no known history of exposure to tuberculosis in the family but both the maternal and pater-

nal grandparents suffered from asthma. The Pirquet test was only slightly positive. The examiner made the following note: "Persistent râles in the right apex after cough." The x-ray film showed considerable evidence of calcification in the region of the left lung hilum. Sputum examination was negative for tubercle bacilli. The temperature record was normal. On November 10, 1925, on re-examination no râles could be elicited. His temperature was normal, he was feeling well. One week later the x-ray examination showed no change. He did not report for re-examination but in the spring of 1932 he was a patient in the Glen Lake Sanatorium with frank pulmonary tuberculosis of the right lung with cavity formation.

In April of 1926 a girl of 11 years was brought to the Lymanhurst Out-patient department because of nervousness. There was no definite history of exposure to tuberculosis, but it was stated that her father was not well. The tuberculin test was markedly



FIG 2 From an x-ray film taken on November 6, 1931, of the same chest as seen in figure 1. Evidence of childhood tuberculosis in right lung hilum, as was seen in 1921 and 1922. In addition there is extensive pulmonary tuberculosis involving the greater part of the left lung and a small area in the fourth interspace on the right side.

positive The x-ray films of her chest showed definite evidence of calcification in the left hilum region, with Ghon tubercle formation in the extreme left base In the left apex was a small area of disease which had the appearance of the adult type of tuberculosis In December, 1928, there was no change in the x-ray film except an increase in the extent of adult type of tuberculosis in the left apex In May of 1930 this disease had extended so as to have become quite advanced and there was evidence of a fairly large cavity in the apex In June, 1930 artificial pneumothorax had been instituted

In July, 1927, a girl of 14 years was brought in for an examination because of exposure to her father who was then suffering from pulmonary tuberculosis The tuberculin test was slightly positive The x-ray film of her chest showed no evidence of disease except at the region of the left lung hilum This was interpreted as the childhood type of tuberculosis In February, 1929, there was a definite extension of this disease into the lung parenchyma, while in May, 1930, following blood spitting, there was definite increase of the shadow How much of this was due to hemorrhage could not at that time be definitely determined However, in December of the same year shadows were making their appearance in the upper part of the left lung In January, 1932, following phrenic exeresis performed at the Glen Lake Sanatorium, the left lung appeared very much improved

In May, 1928, a girl of 14 years was brought for an examination because of prolonged intimate contact exposure to a sister who was suffering from pulmonary tuberculosis There were no symptoms The x-ray film of her chest showed the childhood type of tuberculosis with beginning calcification in the left hilum region (figure 3) In July of 1930 she had an attack of pleurisy and during the same month she had a frank pulmonary hemorrhage X-ray examination of the chest in August, 1930 (figure 4), showed a definite adult type of tuberculosis involving the right lung In March, 1931, this disease was partly under control by artificial pneumothorax Disease later appeared in the left lung (figure 5) At this time, April, 1932

her general condition is good as she continues on bilateral artificial pneumothorax (figure 6)

A belief has been very firmly implanted in the minds of tuberculosis workers that it is good to have a positive tuberculin reaction by the time one reaches adult life In the literature one sees reference to the belief that it is an unfortunate individual who passes into adult life without a positive tuberculin reaction and then comes in contact with tubercle bacilli Opinion has it that it is such cases who develop military tuberculosis or galloping consumption More than a decade ago, I attended a national meeting where one of the world's outstanding authorities of the day discussed this subject In response to the question, if it were possible for a child to escape tuberculous infection and grow to adult life, say twenty or twenty-five years, still negative to the tuberculin test, what would be the outcome if he then came in contact with tubercle bacilli The answer was something like this That individual would be most unfortunate he would develop a rapidly progressive generalized tuberculosis and die of what is known to the public as galloping consumption Upon what scientific evidence was this statement based? Had anyone followed such a case reacting negatively to the tuberculin test into adult life to observe the result? Apparently not So far as we have been able to determine the statement was based largely upon personal opinion

Changing conditions with reference to tuberculosis have brought about the time when tuberculous infection is not universal among young adults This fact gives us opportunities to study

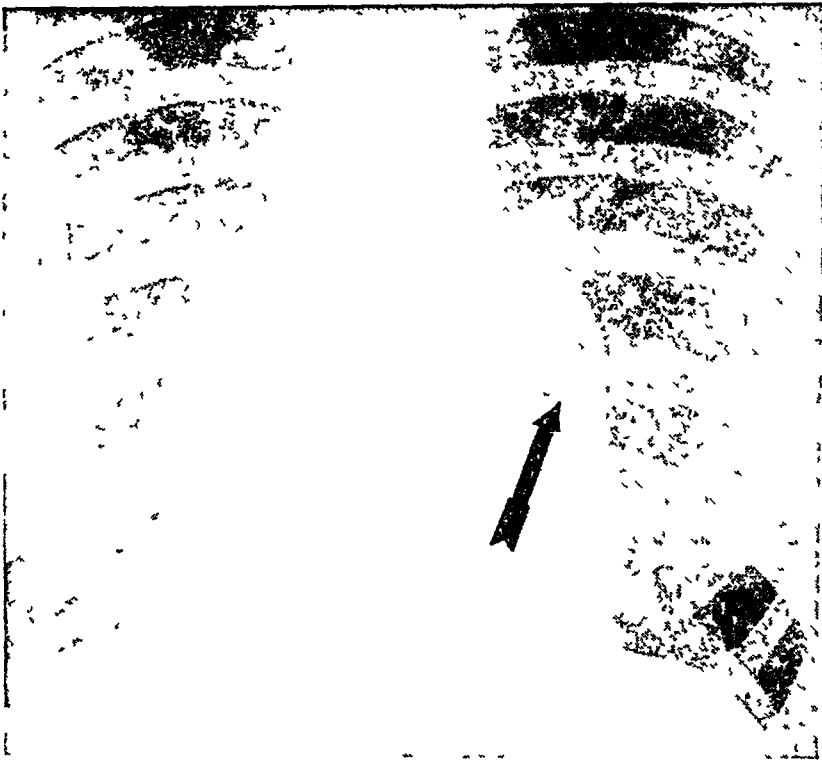


FIG 3 From an x-ray film taken on May 14, 1928, of the chest of a girl of 14 years Intimate contact exposure Tuberculin test positive Childhood tuberculosis with beginning calcification in the left hilum region

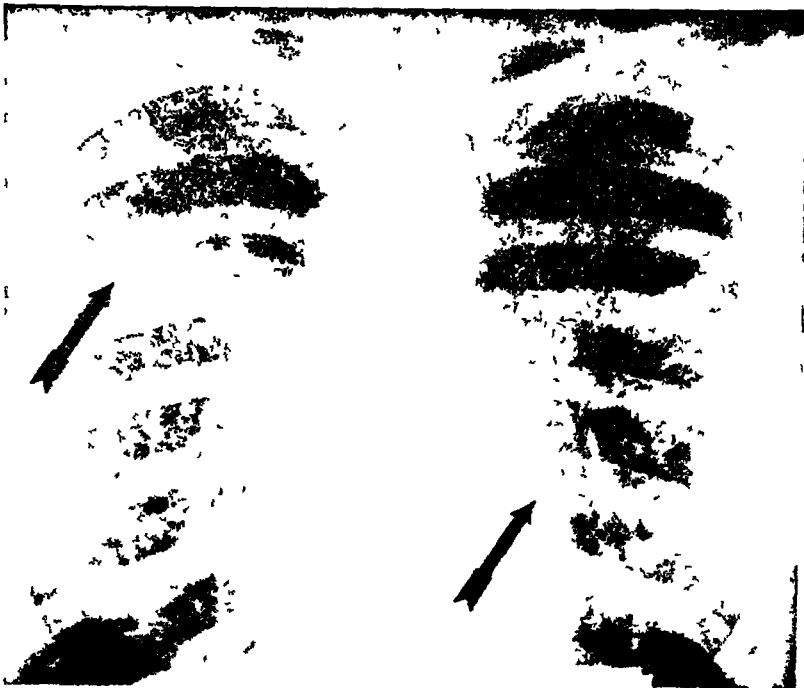


FIG 4. From an x-ray film taken on August 26, 1930, of the same chest as figure 3 Childhood tuberculosis of left hilum region The adult type of tuberculosis has now made its appearance in the right lung.

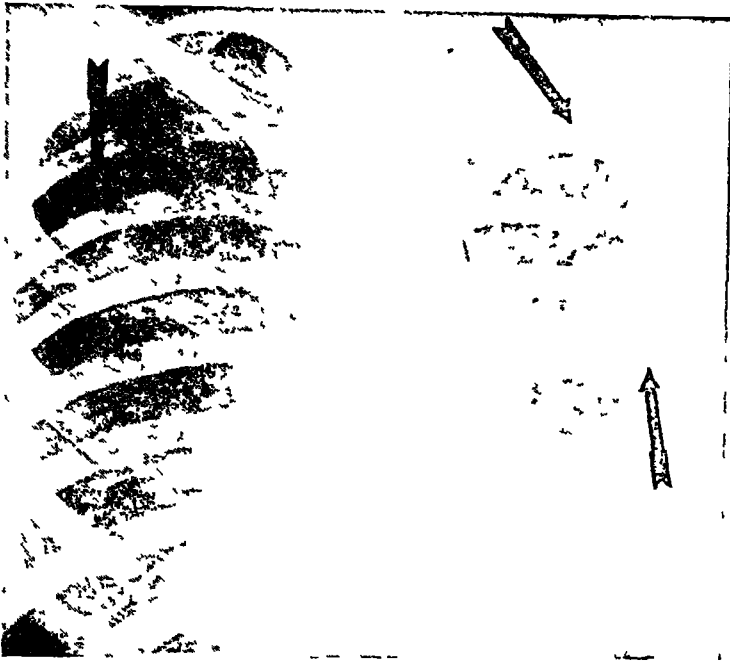


FIG 5 From an x-ray film taken on October 6, 1931, of the same chest as figures 3 and 4 Artificial pneumothorax has been instituted on the right side and disease of the adult type has made its appearance in the left lung



FIG 6 From an x-ray film taken on December 1, 1931, of the same chest as figures 3, 4, and 5, after artificial pneumothorax had also been instituted on the left side

those persons who react negatively until they reach adult life. There are now communities, in fact, we believe good sized areas in the United States, where such individuals may pass through life's span without becoming infected with tubercle bacilli. Certain of these individuals enter hazardous occupations and professions. In other words, in the preparation for certain professions they are greatly exposed to tuberculosis. I refer particularly to the nursing and the medical professions. Here we have been able to observe young adults entering schools of nursing and medicine with negative tuberculin reactions and to test them with tuberculin and examine them by x-ray films periodically. Over and over we have seen the students of nursing and medicine reach the junior or senior years with negative tuberculin reactions, then following exposure to tuberculous patients some of them present positive tuberculin reactions. Usually they are positive to a three plus degree with a 0.1 mgm of tuberculin, indicating a high degree of allergy. At this time the x-ray film examination is usually negative. As time passes, however, often in the complete absence of symptoms, there appear in the chests of some of these recently positive reactors definite evidences of disease. If the focus is in the lung parenchyma, it may remain small or there may develop around it a considerable area of collateral inflammation. So far as we have been able to determine, the lesions are not apparently different than those we have observed develop from the first infection with tubercle bacilli in the chests of infants and children. From our series, however, we are inclined to believe that

pleurisy with effusion occurs somewhat more frequently in young adults than in children. However, our series is not sufficiently large nor have our observations been made over a sufficiently long period of time to make a final statement on this point. Suffice it to say that in the group we are following, we have not seen one patient develop galloping consumption.

CLASSIFICATIONS

When Lymanhurst began, there were many names in use for lesions produced by first infection type of tuberculosis. Such names as juvenile tuberculosis, primary complex, Ghon tubercle, hilum tuberculosis, tracheobronchial lymph node tuberculosis, and epi-tuberculosis were in use. The result was that confusion reigned. No one was entirely certain as to what type of case other workers were considering. A special committee of the American Sanatorium Association in 1929, adopted the term, "childhood type of tuberculosis," and gave definite description of this type. Since that time we have had a common name which is aiding greatly in arriving at a better understanding of the first infection type of tuberculosis. At Lymanhurst, we reclassified our records. Our present classification consists of:

1. Negative to tuberculosis. In this group are placed those children who are negative to the tuberculin test when a full milligram of tuberculin has been administered intracutaneously, and who have no other abnormal findings due to tuberculosis.

2. Primary tuberculous infection. This group consists of those children who react positively to the tuberculin

test but in whom no evidence by x-ray, physical, or laboratory examinations can be obtained of tuberculous disease. We feel certain that each of them has a lesion and in reality, therefore, has tuberculous disease, but by our present methods of examination we are not able to demonstrate its location.

3 Childhood type of tuberculosis. In this group the children react positively to the tuberculin test and in addition have some evidence, usually by x-ray, of the location of the focus or the foci. The lesion may be represented by a shadow indicating an inflammatory process which is progressing, stationary, or receding. Again it may be represented by shadows indicating deposits of calcium. These lesions need not necessarily be in the chest. When evidence of calcium deposits is found in lymph nodes anywhere, particularly in the cervical region or in the mesentery, the classification is that of childhood or first infection type of tuberculosis.

(a) Those with the inflammatory stage when we first see them, progressing, stationary, or receding. If receding, some workers speak of them as the resolving childhood type of tuberculosis. Clinical activity and progression of such lesions are difficult to determine at the first examination, since, in our experience, the most of them have caused few or no symptoms. Of course, they are all active pathologically.

(b) Consists of those lesions in which deposits of calcium can be demonstrated by x-ray film examination. At one time, we spoke of these as healed tuberculous lesions but observation has led us to believe that no

one but the pathologist can make such a diagnosis. Pathologists have pointed out repeatedly that the deposits of lime which we formerly believed actually encased and walled off foci of tuberculosis are usually surrounded by caseous material. Therefore, we never give a case with such a finding a better rating than latent. There may exist an interval of considerable time between *a* and *b*, when the x-ray film examination is almost or entirely negative. If the child is examined for the first time during this interval, there is a strong likelihood that the x-ray report will be negative. At some subsequent time, the x-ray will show deposits of calcium in the area formerly occupied by the disease in its inflammatory stage in the lung parenchyma and in the regional lymph nodes about the lung hilum. The time interval between the development of the inflammatory process and the almost simultaneous enlargement of the regional lymph nodes and the deposition of calcium in these lesions varies a great deal with the individual. The shortest period of time I have seen reported in the literature, is four months. In most of our cases a much longer interval has existed.

4 Adult type of tuberculosis. In this group, we have placed all of the definite clinical forms of tuberculosis whether the lesions appear in the lungs, bony framework, or elsewhere.

Thus we use only four groupings as far as diagnosis is concerned. From the standpoint of the stage of disease and activity, we subdivide group 3 into those with the childhood type of tuberculosis *a* and *b*. We have subdivided the cases with pulmonary tuberculosis according to the classification

adopted by the American Sanatorium Association and by the National Tuberculosis Association

We are dissatisfied with the terminology of the second division. We are so firmly convinced of the specificity of the tuberculin test that we feel that every child reacting positively has in his body somewhere, a tuberculous focus. Although our methods of examination are not sufficiently refined to locate many of these foci in the living body, nevertheless, we are convinced of their presence. Therefore, we are of the opinion that every one of these cases should be classed as a case of the first infection or childhood type of tuberculosis without demonstrable lesions. A place in our classification with a sharp line between so-called tuberculous infection and tuberculous disease is not warranted by our experience. We believe that work in tuberculosis control has been definitely retarded because of this sharp dividing line. How easy it is to examine a child who has reacted positively to tuberculin and fail to find any symptoms or evidence of disease even by stereoscopic x-ray films, and then pass over the condition lightly by saying, "This means nothing except that the child has been infected!" In reality, it means that there is a focus of disease present which may have resulted in no symptoms or symptoms so subliminal as not to have been detected, or mild detectable symptoms which were mistaken for those of some other disease condition. In our opinion, it is better to face the issue squarely and recognize the existence of foci of tuberculosis in all cases reacting positively to the tuberculin test. It

then becomes a question of extent of lesion. Fortunately for the human family, many such lesions apparently are never greater than microscopic in proportion, therefore, are never demonstrated in the living body, but in a certain percentage of cases, and no one knows with certainty what this percentage is, the lesions become macroscopic in size and if located in a part of the body which lends itself to x-ray film examination, will cause a shadow which can be demonstrated on the x-ray film. Such cases, then, fall into group 3. In some cases reacting positively to the tuberculin test whether the first infection type lesion is or is not demonstrable, there later appears the destructive type of tuberculosis, which classes them in group 4.

We now admit to the Lymanhurst School those children who have the childhood type of tuberculosis and minimal lesions of the adult type, provided such cases are not spreaders of tubercle bacilli. We are of the opinion that children who have recently become positive reactors to tuberculin should have the advantage of such an institution.

The Lymanhurst School does not provide the last three years of high school. Inasmuch as it is during the high school age that so many children fall ill with the adult type of tuberculosis, we believe that such a school should include all the grades through high school. However, since in the latter part of the high school course most children are beyond the compulsory school age, the problem becomes complicated.

In the Lymanhurst School the treatment is very simple. This institution is

a day school and no provisions are made for any child to remain longer than the usual school hours. When a child is admitted the first thought is to prevent further exposure to tuberculosis. If an open case exists in the home, one can not expect good results until the contact is broken. This must be considered the first principle in the treatment of the childhood type of tuberculosis. Careful attention is paid to the diet, in order to insure a sufficient amount of growth-promoting, energy-producing, and tissue-building foods. Cod liver oil is used as a food in order to insure a sufficient amount of vitamins A and D. After providing foods to provide energy, an attempt is next made to conserve it through the regulation of games at the recess periods and through a special rest hour immediately after lunch. Close medical and nursing supervision are provided, as we feel this is second only to the regulation of energy expenditure. Through ten years of observation of cases with the childhood type of tuberculosis, we are convinced that institutional care such as that provided by the sanatorium or general hospital is not necessary nor do we believe that special methods of treatment such as collapse therapy are indicated in the childhood type of tuberculosis. When our children develop the adult type of disease, however, we are of the opinion that the most drastic methods of treatment now employed should be instituted. We thoroughly agree with Chadwick in the use of collapse therapy even in minimal cases of the adult type of tuberculosis in girls and boys of the 'teen ages. When such cases develop and show a tendency

to spread and to break down, we refer them to their private physicians if they are able to pay for medical care, otherwise, they are referred to the University of Minnesota Hospital, the Glen Lake Sanatorium, and the Minnesota State Sanatorium. When they have been satisfactorily treated they may then return to Lymanhurst to complete the grades taught there.

SUMMARY

1 In the diagnosis of the childhood type of tuberculosis the tuberculin test and x-ray film examination are superior to all other aids.

2 The best type of tuberculin test is the intracutaneous method of Mantoux, inasmuch as its administration results in a greater number of positive reactors and it allows a measure of the dose of tuberculin.

3 Observations at Lymanhurst lead us to believe that the intracutaneous test is so specific that it constitutes a very fine tuberculosis screen. Therefore, it can be used to great advantage in the selection of children for further studies. If the tuberculin test is negative to a full milligram of tuberculin, one need go no further as far as tuberculosis is concerned, except in rare cases. If it is positive, one should then seek the location of the disease.

4 The x-ray film aids us in locating more foci of tuberculosis in the human body than all other phases of the examination combined. Indeed, it is the only phase of the examination which locates the childhood type of tuberculosis in any considerable number of cases.

5 The x-ray film is a coarse screen when compared with tuberculin mas-

much as we are rarely able to detect lesions by its use in more than 20 to 25 per cent of the children who react positively to this test

6 Among 4,031 children reacting negatively to the tuberculin test, there was evidence of questionable to definite childhood type of tuberculosis in 2.79 per cent while among 4,737 children reacting positively to the tuberculin test, such evidence of the childhood type of tuberculosis was found in 22.91 per cent. Among the 4,031 negative tuberculin reactors the adult type of tuberculosis was found in .05 per cent, while among the 4,737 positive reactors the adult type of disease was found in 1.26 per cent. Among our negative tuberculin reactors, no case of tuberculosis of the bones and joints was found, while among the positive reactors 52 per cent was found.

7 In our experience the infant has been found to have an excellent tolerance for tubercle bacilli. The factors which seem to determine whether he survives or succumbs are dosage and continued exposure.

9 Our observations have convinced us that only those children with the first infection type of tuberculosis develop the adult and destructive type. Therefore, we can not see our way clear to consider the first infection type of tuberculosis as a protection to the child.

10 In a group of young adults re-

acting negatively to the tuberculin test, who became positive reactors following exposure to tuberculosis, we have been able to watch the lesions make their appearance on the x-ray film and to follow them. This group has convinced us that such cases, reaching adult life before becoming infected with tubercle bacilli, do not develop galloping consumption as was formerly thought. Therefore, in our opinion the longer the first infection type of tuberculosis can be prevented in the human body, the better. The ultimate goal should be to reduce the possibilities of exposure so that the span of life may be lived without the first infection type of tuberculosis appearing in the bodies of most people.

11 The childhood type of tuberculosis usually comes under control without treatment. We believe that it rarely, if ever, kills as it occurs in nature, and we are of the opinion that the vast majority of such cases do not require hospitalization. Protection from further exposure to tubercle bacilli, energy producing foods, conservation of energy, medical and nursing supervision, such as may be provided by special schools for tuberculous children, is all that is required. When the adult type of tuberculosis appears, if the home conditions are not good, sanatorium or hospital care is indicated, and such special treatment as collapse therapy is none too drastic.

Friction Rub over the Liver in a Patient with Subacute Bacterial Endocarditis

By MILOSH KASICH, M D, *New York, N Y*

THE patient, B S, 15 years of age was admitted to the New York City Hospital March 21, 1930, complaining of pain in the chest, cough and shortness of breath. The family history was unimportant. He had been an invalid since childhood and when he was two years old his mother was told that he had "heart trouble." For many years his activity had been limited because of dyspnea upon the slightest exertion. There was no history of rheumatic fever or of chorea. He had had occasional sore throats. Tonsillectomy was performed about five years ago.

His present illness began about five months before admission. Dyspnea, which had always been present to some extent, became more severe, and grew progressively worse. He had been bed-ridden for the last two weeks. Several days before he began to complain of pain in the right chest, and in the right upper quadrant. The abdominal pain was described as burning in character. A distressing cough, with blood streaked sputum, had been present for the last week. The pain in the chest was aggravated by coughing.

Physical Examination An acutely ill, undernourished boy, lay propped up in bed, breathing with difficulty. Eyes, ears, nose and throat were negative. The veins in the neck pulsated. Anteriorly, both lungs were clear. There was a friction rub in the right axilla. Both bases posteriorly were dull. The precordium was bulging and a diffuse impulse was felt along the left sternal margin. The apex was in the sixth interspace, 11 cm from the midsternal line. A double murmur, heard best in the region of the apex, was transmitted over the entire precordium. The rate of the heart was 128, and regular. The blood pressure was 110/55. The abdomen was soft and not distended. The liver was felt two fingers below the right costal margin, it was not tender and did not pulsate. The spleen was not palpable. The fingers were slightly clubbed. There was no ankle edema. Knee jerks were equally active. Examination of the blood showed Red blood cells, 4,050,000, hemoglobin, 75 per cent, white blood cells, 14,000, polymorphonuclears, 75 per cent, lymphocytes, 25 per cent. The roentgen-ray examination of the chest showed marked stasis of the pulmonary fields with some areas of consolidation at the right base broncho-pneumonic in type. The heart

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shadow was typical of mitral stenosis.

The diagnosis made at the time was Chronic rheumatic endocarditis, adhesive pleurisy, bronchopneumonia, subacute bacterial endocarditis with pulmonary infarction

Progress of the Case. The boy was put at complete rest. He was given a light diet, forced fluids and sodium salicylate, 20 grains three times a day. His condition remained essentially unchanged. The temperature was intermittently febrile in character, rising to 104.4° C, and occasionally falling to 99°. On March 26 an area of consolidation was found on the left side in the posterior axillary line. On April 4 the patient was much improved. The chest signs, however, did not clear up. On several occasions he expectorated small amounts of blood, and twice developed red, painful joints, the knees and elbows being involved. He frequently complained of substernal pain. Blood culture on April 26 was negative. The urine was frequently examined for red cells, but none were found. On May 1 another blood culture was taken which also proved negative. On May 18 it was noted that the fever was continuing, the liver was larger and more tender. The splenic area was tender on percussion, suggesting either infarction or intense congestion. Although a positive blood culture, petechiae, and a palpable spleen were lacking numerous infarctions in the lungs and spleen and the continued irregular fever pointed to subacute bacterial endocarditis. On June 5, at a point two inches to the left and three inches above the umbilicus a loud friction rub was heard. This area corresponded to the enlarged right lobe of

the liver. The sound was influenced by both the heart beat and by respiration and was localized over an area about the size of a twenty-five cent piece. The entire liver was very tender and the abdominal muscles were rigid.

The patient lost ground steadily and died on the morning of June 7.

Autopsy (Dr. James Lisa) The chief findings at autopsy may be summarized as follows:

- 1 Chronic rheumatic endocarditis, with stenosis of the mitral and tricuspid valves
- 2 Subacute bacterial endocarditis, with many hemorrhagic areas over the endocardium
3. Marked atherosclerosis of the pulmonary artery
- 4 Multiple areas of infarction in both lungs
- 5 On the upper surface of the right lobe of the liver almost in the midline, there was an area about the size of a silver dollar, dull, and covered with fibrinous exudate. The corresponding area of the parietal peritoneum showed a similar change.
- 6 Chronic congestion of the spleen with no infarction demonstrable.

SUMMARY

A case of subacute bacterial endocarditis is reported which during the course of the disease developed a friction rub over the liver. Post-mortem examination showed the rub to be due to an area of peritonitis over the liver. The mechanism of the production of the sign is most probably a metastatic hematogenous infection. Such a finding has not been previously reported.

The Migraine Syndrome

By OLIVER T. OSBORNE, M A , M D , F A C P , *New Haven, Connecticut*

A VERY interesting research on migraine by R. M Balyeat and H J Rinkel (*ANNALS OF INTERNAL MEDICINE*, 1931, v, 713-728) causes me to offer the results of my long study of the causative factors of this painful disease or syndrome. Also, I believe that we should study this syndrome from all angles.

In the first place, I agree with the above writers that the cyclic vomiting of young children is a migraine symptom. Secondly, I also find that those afflicted with migraine very commonly have their attacks become less frequent or entirely disappear after about forty-five years of age. I attribute the cessation of the migraine at this time to presbyopia and the consequent use of glasses that relieve eyestrain.

So-called migraine is a condition that may be defined as a pain which begins at one side of the head, and is often termed "sick headache" because it is associated very generally with nausea and vomiting. These attacks are likely to occur periodically, more or less regularly. It is a question whether this kind of headache should have a distinct name. It is not an entity but a syndrome. It has been considered a neurosis, and it is true that people with a neurotic tendency are more likely to have this sort of headache than are phlegmatic individuals. In the writer's

opinion, in the vast majority of cases of so-called migraine imperfect eyes, and therefore eyestrain, is the cause. In fact, after forty-five years of practice as an internist (half of which time was spent in general practice and the latter half as consultant in internal medicine) he has never seen a case of typical migraine that did not have optic defects and consequent eyestrain as a cause.

Migraine is said to be hereditary, as a matter of fact it is only the neurotic tendency and defective eyes that are handed down in families. The type of eye that is inherited is astigmatic, most frequently associated with hypermetropia, and such defects cause eyestrain and consequent headaches. This type of headache is very likely to begin in early childhood, especially when the child first goes to school.

These headaches are referred to every cause that can be considered except the one to which it is due, namely, eyestrain. There is no question that overeating, indigestion, constipation, hyperexcitability, increased thyroid secretion, fever from any cause, disturbances at the beginning of menstruation, mental excitement, or anything else that is abnormal or excessive will cause a headache in these individuals. But the reason they cause a headache in these persons lies in the presence of optical de-

fects, and the reason that the pain generally occurs more on one side of the head than on the other is because the eye on that side is more defective and there is a greater strain of the eye muscles on that side. Late hours and prolonged use of the eyes will precipitate an attack of headache, generally the next morning.

Nasal pressure, adenoids and disturbances of the ear may all aid in causing so-called migraine. Also there is a great tendency to periodicity, possibly from coincident pituitary disturbance. This periodicity may be so imbedded in the constitution of the individual that no matter what is done toward correcting the eye defect, recurrences of the migraine will take place. Therefore the sooner in the life of the individual the eye defect is corrected, the less likely are such attacks to recur, *provided the correction is perfect*.

While migraine has been so long considered a distinct disease of the nervous system because there are so many associated symptoms that are not headache, still, a study of the eye reflexes will show that they are all dependent upon an abnormal condition in one or both eyes.

The time of day and the particular irritant, or disturbance, that starts the eyestrain headache varies with the individual. Some wake up in the morning with their headache from the eyestrain of the day before. Others have the headache in the later part of the day and it stops soon after the individual goes to bed. Others have their headaches begin in the morning and grow gradually worse until they are completely prostrated.

Probably the most frequent cause of intense eyestrain headache is astigmatism, generally that which is associated with hypermetropia. Hypermetropia alone can give recurrent headaches, and myopia less frequently. Not infrequently, the greater the defect, the less frequent the headaches, because the eye may refuse to correct the image, or the image of one eye may be entirely eliminated, the patient using only one eye and ceasing to attempt binocular vision. Therefore, many times the person with a minor optic defect, whose eye muscles always strive to give him a perfect image, is the one who has the most eyestrain headaches.

A frequent prodromal symptom of an attack is a craving for food, a sort of hunger, and frequently a hunger for meat. This is the same reflex which, after the headache begins, goes to the other extreme and causes nausea and vomiting. In the intermediate time between the craving for food and the nausea and vomiting, digestion is inhibited and food may lie in the stomach for hours, to be finally vomited, undigested, often with excessive acidity and with regurgitated bile.

Any prolonged, close use of the eyes without normal intermission, as working for hours without food, reading late in the evening, playing cards; embroidering or sewing too long, going to the theater or movies, or anything that uses the eyes for long periods of time without rest, will cause these individuals to have a headache. Many persons, even if glasses that correct the eye defects are worn have headache from the above causes.

Sometimes this "eye tire" is corrected before it has gone too far by

eating some simple food, the blood goes to the digestive organs and the head is relieved of congestion and tire. Some individuals can not eat at all, and will lose their appetite entirely, with the least headache.

Sometimes the most intense headache is caused by distance vision, as when the individual goes into the mountains and looks up a great deal, or when he goes to the seashore, or is on the water, and watches the waves.

It is very easy to determine that the headache is due to eyetire by careful questioning.

First, what is the patient's work, how long does he use his eyes, what does he like to do and what does he dislike to do, does going to the movies, to the theater or to church cause headache, does reading the poor print of the newspapers, playing cards, sewing or other eye-work cause headache, does he become car-sick, or trolley-sick or is he rested by riding, does he get a headache at a ball game or by watching a parade, does she get a headache from shopping? The study of the answers to all of these questions will convince the interrogator that he is, or is not, dealing with an optic defect.

The majority of individuals, until they have learned that their headaches are due to eyestrain, attribute the headache to almost anything they may have done last or eaten last. They change their diets, they omit this or that food, or they call it nervous tire and nervous headache, or they lay the headache to some condition, as bad air, or being shut up and not getting out-of-doors, or to menstruation, or to most any of the things that occur in life. While these are doubtless aggravating

factors, the headache would rarely occur if eyestrain were not present.

Some peculiar cases do not have headache with defective eyes, but have stomach reflexes of all kinds and descriptions, indigestion, flatulence, pyrosis or hyperacidity, or they have cardiac disturbances, as faintness, palpitation, or irregularity of the heart beats. They may be treated for these conditions by washing out the stomach, by heart tonics, etc., etc., when the cause is really and only, many times, eyestrain, which, when corrected causes these abnormal symptoms to disappear.

The most intense eyestrain headaches, migraine attacks, are caused by astigmatism, and the muscles most concerned with correcting abnormal meridians of the eye are the superior and inferior oblique. These rotate the eye so that even with imperfect rotundity a perfect image is seen. The superior oblique muscle goes to the upper internal angle of the orbit, and this is a point, very generally, of intense pain in eyestrain headache, showing that this muscle becomes tired and irritated and apparently goes into spasm much as a wry-neck or other muscle cramp. The inferior oblique goes backward and out beneath the inferior rectus muscle, and is inserted in the sclerotic membrane between the optic nerve entrance and the attachment of the external rectus. When this muscle is strained the pain seems to be more deeply seated back of the eye, and it also, doubtless, goes into a condition of cramp or spasm.

As above stated, this eyestrain headache may be confined to one eye, but more frequently it goes to the other eye.

in sympathy, or the other eye may also have defects, but as generally one eye is worse than the other, the headaches are likely to start as a one-sided condition.

Depending entirely on the intensity of the spasm and the pain and the neurotic tendency of the individual, other nerves take part in the paroxysm, and there may be pains in the nose, in the face or around the ear, and frequently there are pains in the back of the neck, and even sometimes down the spine, with slight stiffening of the muscles of the back of the neck, showing the great seriousness of reflex conditions from the hypersensitive nerves of the eye. The pain may be so severe as to cause groaning. Sometimes, even in the beginning, it is so intense as to cause faintness and a weak pulse, especially if mental control of the condition is continued too long without going to bed and completely relaxing. When this autosuggestive control lets up and the patient gives in, the pain seems more intense for a time. Sooner or later, in many patients, nausea and vomiting occur, and the patient is said to have a "sick headache", which is laid to something that he has eaten, which can be only a contributory cause to this kind of a headache.

Many individuals learn to take a quickly acting cathartic, and after it has acted, as the headache soon stops, they attribute the condition entirely to gastro-intestinal disturbance and to constipation. While there is no question that benefit occurs from free action of the bowels as well as from evacuating the stomach, in relieving congestion in the head, constipation is not the cause of this kind of headache. Headaches from constipation are of the

dull variety, are more general and are never intense. The same is true of liver insufficiency headache.

The patients who vomit profusely and have terrible nausea and retching become very faint, pale and almost pulseless at times. Soon after this condition occurs the pain will generally cease, relaxation of the muscles occurring, the spasm stopping, and the head is relieved. Sometimes, therefore, the more intense the vomiting the quicker the "migraine" is over. How absurd it is to consider that the stomach condition had anything to do with the cause of the headache is shown by the fact that these individuals can, within a short time, sometimes in an hour or two, eat a good meal, enjoy it and retain it.

Those individuals who have eyestrain headaches without nausea and vomiting can generally keep about all day and fight the headache, and if their glasses are correct, or if they change glasses to those that are correct, may even get over the headache while continuing to work.

Many of those with even a mild form of this headache have cold hands and feet while the headache is in evidence, showing vasomotor spasm. It is quite possible that some of these headaches occur with some of Raynaud's syndrome symptoms. Spasm of blood-vessels may occur as well as the muscle cramp of the eye muscles.

During or preceding these headaches there is frequently an increased amount of urine passed. The urine may be hyperacid, and is generally of low specific gravity. The surface of the body is often cold at the same time, showing contraction of peripheral bloodvessels.

Before the onset of the eyestrain headache there seems to be a tendency to hyperacidity of the system, often stomach hyperacidity, and extra-acid urine, with probably a lessened alkalinity of the blood. Hence it is advisable when premonitory symptoms of these headaches are developing to give a cathartic and to push alkaline treatment.

To repeat, in eyestrain headache or migraine there is often spasm of the oblique muscles of the eye and probably frequently a spasm of the blood vessels of the eye and other parts. This is the reason that anything that reduces this spasmodic condition of the muscles or bloodvessels improves or stops the headache, therefore the advantage of coaltar drugs. Antipyrine, acetanilid, phenacetin, pyramidon and aspirin are the drugs that enter largely into all patented medicines that are sold to cure headaches. Many a sufferer from headache acquires a habit of taking one or more of these drugs, to his or her detriment, as they are all more or less debilitating, all weaken the heart, all tend to cause anemia, and all are muscle depressants. Of course any strong narcotic will stop the headache, as morphine or codeine. Some persons have even inhaled chloroform to stop the terrible pain from an eyestrain headache.

Nature's method of terminating such a headache, when not assisted by drugs, is by the profound nausea causing sufficient muscle relaxation and circulatory depression to relax the spasm of the bloodvessels and muscles that are in trouble. Sometimes the headache ceases almost magically, almost instantaneously. At other times the pain

gradually disappears. If nausea and vomiting do not occur, a hot foot bath to take the blood from the head, or hot water bags around the body, or a hot water bag directly over an eye may cause relaxation sufficient to relieve the spasm and stop the headache. Some individuals learn to take a large dose of alcohol and obtain relaxation of the spasm and dilatation of peripheral vessels, and in this manner get relief.

Some milder forms of this headache last all day until the sun goes down and the light is less, and then relaxation occurs and the headache ceases. Others who do not have vomiting with the attack have the headache persist until after a night's sleep. Most patients during this kind of headache seek a dark room and wish perfect quiet, hardly desiring anyone to speak to them, unless they have serious cardiac depression, almost a syncope, when they wish assistance. They are even so faint, sometimes, that they feel they may die. Such prostration and cardiac weakness may be helped by large doses of alcohol, especially gin, or by black coffee, if they are retained.

Sometimes excruciating pain is helped only by a hypodermic of morphine. Of course such treatment is reprehensible, lest a habit be formed, but the intensity of the pain and the reflex action on the heart, almost to the point of heart failure, occasionally requires such treatment.

Not infrequently an effervescent mixture of phenacetin or other coaltar drug, or a dose of aspirin, or of a coaltar depressant combined with caffeine will help headaches, and many patients become addicted to taking bromoseltzer.

Curative treatment of the condition means the determination of the exact cause, and since the most frequent cause is eyestrain, an absolute correction of the optic defect, that is *correct* glasses, in *correct* frames, *correctly* worn will make the headaches infrequent, and in many cases cure the condition

The oculist should ascertain the kind of work the individual does, and determine what kind of glasses (especially when presbyopia is present) should be given the person, and whether he shall wear the glasses for near work only or all the time. All this must be carefully determined. The lenses must be perfectly ground, the frames perfectly fitted to the face, and if the individual has astigmatism probably the glasses must be worn constantly. The kind of frames is important. They must not be such as readily get out of adjustment. The patient should be told by both oculist and optician and by his physician that maladjusted lenses are as bad as no lenses at all, or even worse,

that his glasses must be frequently re-adjusted, that his eyes will change, and that in from a few months to a year or two, he will probably need a change of lenses

It is also essential that the patient should understand that the oculist's science is not entirely an exact one, and that he may not be able to determine the correct lenses at first, any more than the physician is able to find at the first visit the exact treatment advisable for some internal condition

In the majority of instances (and it should be noted that eyestrain headaches begin during childhood in a large number of cases) the headaches will be cured by proper glasses. Frequently most of the dissociated reflex effects, such as indigestion and heart upsets, are cured by correct lenses

It must not be forgotten, however, with the above emphasis upon eyestrain, that many headaches are due to endocrine gland disturbances, and that correction of these insufficiencies prevents the headaches

The Trend in Cerebral Localization

By LEWELLYS F. BARKER, M.D., F.A.C.P., *Baltimore, Maryland*

THERE is no more fascinating subject in the whole of medicine than the study of the activities of the human brain. This topic has engaged the interests of some of the best workers in medicine—anatomists, physiologists, clinicians, pathologists, experimental workers, psychologists—especially during the last hundred years. Really great progress has been made, but, despite the advances, we are still only at the threshold of the knowledge of many of the cerebral functions.

We use the term "localization" in somewhat different ways. Thus, we think of localization of function, we think of localization of lesions in certain diseases, and, again, we think of localization from the clinical standpoint of determining the sites of lesions.

The spadework in this domain was done by the anatomists, who taught us the topography of the surface of the brain, later, the histologists worked out the great fiber tracts within the brain.

On the lateral surface of the brain, the central sulcus separates the frontal from the parietal lobe, the fissure of Sylvius separates both from the temporal lobe. The motor area includes the anterior central gyrus and the feet

of the frontal gyrus. Broca's area for motor aphasia lies in the operculum, at the posterior part of the third left frontal gyrus. The somesthetic area lies mainly in the posterior central gyrus. The primary auditory center lies in the posterior part of the first temporal gyrus and in the transverse temporal gyri, with Wernicke's area for sensory aphasia (word-deafness) just below it. The gyrus angularis is an area important for reading and writing, since lesions there may cause alexia and agraphia.

On the medial surface, we remember that the lobulus paracentralis is an important motor area for the lower extremity, that the region of the calcarine fissure is concerned in vision, a unilateral lesion causing cortical hemianopsia, and that the uncus has to do with the perception of taste and smell. Tactile agnosia is usually associated with lesions of the middle third of the two central gyri, auditory agnosia with bilateral lesions of the superior temporal gyri and optic agnosia with lesions of the lateral parts of the occipital lobes. Lesions that cause apraxia may be either cortical or subcortical.

Meynert did a great service when he developed the idea of projection fibers as contrasted with association fibers. He showed us how certain long fiber tracts run from the cortex downward and others from below upward to the

Abstract of remarks made at the General Session of the American College of Physicians, Baltimore, March 24, 1931. Illustrated by lantern slides.

cortex and that they are massed together in the posterior limb of the internal capsule, the descending motor projection fibers in the anterior two-thirds of this posterior limb and the ascending sensory projection fibers in the posterior third. Thus, from before backward in the internal capsule we have the motor fibers for the face, head, arm and leg and, behind them in turn, the fibers for sensation. The projection fibers radiate from and to the cortex through the corona radiata.

During the last ten years, great progress has been made in the analysis of the functions of the fibers that extend between the corpus striatum and the midbrain, pons, medulla and spinal cord. No small part of this analysis has depended upon work done in connection with epidemic encephalitis and its sequels.

Surgeons who explored the brain in the search for tumors were able to localize with great accuracy certain points whence particular movements of, for instance, a thumb, or a single finger, can be elicited by electrical stimulation.

The projection fiber studies of Meynert were corroborated and greatly extended by the embryological researches of Flechsig of Leipzig, who showed us that the projection fiber tracts within the brain become myelinated long before the association tracts do. By suitable staining, the sequence of the myelination of the fibers can be determined. Thus, the fibers from the motor area of the anterior central gyrus and those to the sensory area of the posterior central gyrus, together with the visual fibers to the occipital lobe and the fibers for taste and smell to the uncus, are among the earliest to become myelinated.

Following upon these careful studies of the grosser structure of the brain came a series of minute microscopic examinations of the different parts of the cerebral cortex. Anyone who studies modern histological sections of the cerebral cortex cannot avoid being astounded by the complexity of organization in each single area. Thus, in a section from the anterior central gyrus, the motor area, one sees at least seven different layers of pyramidal cells of different sizes and arrangement.

Systematic examinations of the whole cerebral cortex from the standpoint of histological makeup have been made and it is possible to divide the cortex into a host of areas corresponding to the different histological pictures presented, though we are very far as yet from recognizing the functional significance of the differences.

Very careful studies have been made, too, of the blood supply of the human cerebral cortex. Personally, I was greatly surprised when I found how close the meshwork of capillaries is, and how different the arrangement of the capillaries is in different parts. You need only examine corrosion specimens after injection of the arterioles and capillaries in the cortex, magnified about 100 times, to realize the complexity. You can see the main arterioles and how they break up into the small meshes of smaller arterioles. On still further magnification of these small vessels, one wonders how there can be room between them for the nerve cells and the nerve fibers! The variations in the density of this meshwork of vessels probably has something to do with the distribution of poisons and of bacteria that are, in certain diseases, distributed to the brain. It, to some ex-

tent, determines the localization of poisons and of bacteria that enter the brain through the blood vessels

Careful studies have been made by Hugo Spatz at the Institute for Brain Research in Munich of the distribution of the lesions of epidemic encephalitis. Though the lesions may be widely disseminated, the distribution is largely in the white matter and in the basal ganglia. This can be no accident, something must determine the localization of the lesions due to the virus in this disease. One factor in the localization may lie in the character of the virus itself, a second factor, in all probability, lies in the blood vascular supply, and a third in varying local disposition of nerve-cells and fibers to the action of the virus or its toxins.

One sees great differences in the localization of the lesions in different varieties of encephalitis and this may be illustrated by reference to the distribution in diffuse periaxial encephalitis, in pyogenic encephalitis, in tuberculous meningo-encephalitis, in the cerebral form of epidemic encephalitis, and in the encephalomyelitic form. You will note that in epidemic encephalitis the basal ganglia are particularly prone to be involved in the neighborhood of the third ventricle and the aqueduct.

In recent years, the contributions of surgeons to cerebral localization through the exploration for tumors and other lesions have been vastly supplemented by the method devised by Dr W. E. Dandy, who injected air into the ventricles or the subarachnoid space and made ventriculograms and encephalomyelograms by x-rays in both lateral and anterior views. By studying the distortions of the lateral ventri-

cle due to pressure, it is often possible to determine the exact position of tumors or cysts, that have not given definite localizing symptoms, and to remove them. The elimination of such space-occupying masses is, in some cases, just as important for differential diagnosis as the discovery of their presence in other cases. One cannot fail to recognize quickly the importance of this method for the diagnosis of hydrocephalus in its various forms and of brain tumors, cysts, and abscesses.

Last month, I was asked to study a girl of 15 who had epilepsy that was supposed to be of the idiopathic type, the attacks having persisted for several years. We made, however, a general neurological examination in the hope of finding symptoms or signs pointing to a focal lesion. In the course of the study, Dr. Angus L. MacLean made a most careful examination of the visual fields and discovered a beginning hemianopsia that involved the color fields more than the ordinary light fields, this pointed to a lesion of the optic pathway somewhere between the chiasm and the visual area in the occipital lobe. This gave the clue that the lesion was in the right half of the skull, probably behind its middle. I asked Dr. Dandy to see her and to decide whether or not to operate after making an air injection.

The arrangement was made with the parents that, if anything should be found during the air injection that warranted operation, they would permit it to be done at once. Dr. Dandy made a small opening in the skull put in a needle and suddenly felt it enter something soft. The air injection was then made and the roentgenograms,

immediately developed, revealed a cyst shown in the lateral view of the skull as in the posterior part of the right side of the brain

An antero-posterior roentgenogram showed that this cyst was of the size of a small orange. The needle had entered the cyst, but had not gone into the ventricle and the cyst did not communicate with the ventricle. Operation was proceeded with at once and the cyst was easily removed. The patient made a quick post-operative recovery and left the hospital at the end of three weeks. She was still having epileptic seizures, but though they may continue for a time, it is probable that they will disappear entirely later on, at any rate, in several similar cases they have done so. That was an interesting example of the possibilities of Dandy's encephalographic method of diagnosis.

The studies of brain tumor and of epilepsy have permitted a charting of the brain surface now that is much more complete than was ever before possible. Our clinical diagnosis of the situation of brain lesions has been greatly facilitated by such studies. The results of actual clinicopathological experience have been far more illuminating than all speculations regarding cerebral localization upon *a priori* grounds.

The psychologists have, in a praiseworthy way, tried to help out clinicians, but they have often been too visionary. You will recall that they have made a whole series of diagrams illustrating their conceptions of how brain centers must be connected with one another, and where the association paths between them must lie. These diagramatists went much too far; most of their

parallelograms and triangles presented in the textbooks are misleading. We must admit that, at present, the whole question of aphasia is still far from being satisfactorily answered. Though the brain area we are taught to look upon as the site of lesions that cause sensory aphasia is sometimes involved, there are a great many so-called "negative" cases and there are many bizarre cases that are difficult of explanation.

Some light seems recently to have been thrown upon cerebral localization by workers in comparative neurology and in experimental physiology. In *Science*, you will find a review by Karl S. Lashley* of the new work upon mass action in cerebral function, with particular reference to the difference between localized function and decentralized function in the brain. Though each part of the brain has its own particular function to serve, it also plays a part, it seems, in mass action, in the dynamic action of the brain surface as a whole.

If you remove a piece of cerebral cortex, you may abolish a certain function that belongs to that particular area, but you also influence certain other nervous functions at a distance, and that second influence appears to depend directly, no matter what part of the brain surface you excise, upon the amount of material that you remove from the cortex. It looks, therefore, as though there were some kind of "dynamic action of the brain surface as a whole", first upon other centers in the brain surface itself and, perhaps still more important, upon the subcortical centers. For example, it is said that the

*Lashley, K. C. Mass action in cerebral function. *Sci.* 1931, lxviii, 245-254.

powers of a rat to learn and to retain what is learned can be greatly influenced by removal of any portion of the brain and that the influence exerted will be in exact correspondence to the amount removed. Learning and retention, in other words, what we call "intelligence", seems to be closely related to mass functions of the cortex.

It may, however, be found that what these comparative neurologists and psychologists are calling "mass function" may be group functions of areas associatively connected throughout this great cortex. We must wait and see. When I think of the immense network of fibers and the millions of nerve cells in the widely distributed cortex, I can-

not help but keep in mind the possibility that many areas probably act together and not in a wholly indifferent way. Multiple groups of cells and multiple groups of association fibers, working together, might easily influence other areas of the cortex and subcortical areas along with them.

The advances thus far made in the study of cerebral localization will certainly be a great stimulus to further study. During the next decade or two we shall, I believe, see remarkable advances in the further localization of function within the brain and they will undoubtedly add to our powers of precise clinical diagnosis.

Editorials

THE SEVENTEENTH ANNUAL CLINICAL SESSION

The program for the Annual Meeting of the American College of Physicians, which will be held in Montreal during the week of February 6, 1933, is nearing completion. The meeting will take place at the height of Montreal's winter season. Those who attended the Minneapolis meeting will remember how well these northern cities are prepared for cold weather. With well heated buildings and taxicabs, the comfort of the guests is assured, and those who come from sections of the country possessing mild climates need have no hesitancy on account of the cold.

The General Meetings will be held in the Windsor Hotel, which is the headquarters and the Clinics will be concentrated in a few of the many hospitals of the city. The local Committee on Arrangements is making every effort to insure a meeting of highest excellence.

The General Program, following up the symposium on visceral neurology, which was so well presented and so enthusiastically received at the San Francisco meeting, will go still further into the physiologic aspects of medicine. There will be several papers dealing with the chemical and physical constitution, and their relationship to health and diseases. In a symposium on endocrinology the hormones from the pituitary, adrenal cortex, ovary and testis, parathyroid and pancreas will be discussed by men who engaged in the research work which resulted in their

discovery. The relationship of the vegetative nervous system to disease in general, will be stressed and the influence of the emotions in altering physiologic reactions will be emphasized. The program will thus stress pathologic physiology, the most alluring field of medical study today, and the field which must be thoroughly explored before we can understand how disease affects the individual. These studies emphasize the fact that "there is a patient who has the disease as well as a disease that has the patient."

Neurology and pediatrics, which have been somewhat neglected in recent programs, will be represented by several papers. Diseases of the heart and blood vessels, which are of such great interest to physicians, both in their practice and from a personal standpoint, will be presented from many angles. Diseases of the chest, including tuberculous and nontuberculous affections, will receive due attention. The latest work on pernicious anemia will be presented along with several other papers on diseases of the blood. There will be a discussion of the rôle of desensitization in the recovery from infectious diseases, and many papers dealing with subjects of general interest to internists.

The Clinical Program will be of the highest standard, presenting many problems of research and demonstrating the high type of clinical teaching for which Montreal is so well known.

(FRANCIS M. PORTER, M.D.,
President American College of Physicians.)

GASTRIC PHYSIOLOGY AND CLINICAL MEDICINE

In recent years medical literature has been rich with reports of studies of the gastric secretion, dealing with the physiological as well as with the clinical viewpoint. These studies have not been confined to the diseases of the stomach but have included many diseases in which the stomach had not been recognized previously as playing such an important part. The diagnostic survey of any severe anemia of obscure nature has come to demand a study of the gastric juice. In any chronic gall bladder or intestinal disorder the secretory and motor response of the stomach has become of interest in the light of newer observations. These researches serve as excellent examples of the correlated application of physiology, chemistry and clinical medicine, indeed, such correlation has been in a large measure responsible for many of the accomplishments of modern clinical investigation.

Symptoms, especially in chronic disease, are expressions of disturbed function. The gastro-intestinal tract is responsive in the production of symptoms in many types of disease, the lesion may be in the gastro-intestinal tract itself or it may be located quite remotely to the segment of the gastro-intestinal tract portraying the symptom. Often there is not any organic lesion demonstrable, the gastro-intestinal symptoms are merely somatic manifestations of a nervous system under emotional stress and strain, a poorly balanced or particularly responsive nervous system. In some patients the nervous system may receive and broadcast the faintest possible stimulus, it may be as poorly equipped to give an enjoyable program of life as

the radio that can not tune out the undesirable broadcast. The clinician must be alert and skillful, and frequently he must use the utmost ingenuity to differentiate the purely functional condition from the organic disease which may be manifest by the same symptom complex. Investigations of physiologic function should light the path to a more comprehensive understanding of such clinical problems.

The study of gastric secretion has enjoyed periods of popularity and enthusiasm for its use in diagnosis. Through the publications of the last few years one can sense the tendency to interpret function rather than to diagnose, by gastric analyses. The advent of histamine into clinical use brought forth new methods and revival of the old methods with critical comparison of the value of each. It has been shown beyond a doubt that histamine is a powerful stimulant of hydrochloric acid secretion by the gastric mucosa. The method of Bloomfield and Pollard¹ has provided gastric juice as nearly in the original state of its secretion as it is possible to obtain (barring swallowing of saliva, gastric retention, or duodenal regurgitation). The extensive work of Bloomfield and his associates, and of many others, has demonstrated what may be expected of the gastric mucosa under the influence of histamine injected subcutaneously. Many publications have contributed a vast accumulation of figures. Up to the present time it has been very difficult to arrive at any definite conclusions on how to use this information clinically. The range of normal seems to be so great that one does not know where pathologic response begins. By some histamine has been considered the most powerful gastric stimulant for fact

acidity Evidence against this is available in the work of Comfort and Osterberg² in which they say "histamine failed to cause a secretion of free hydrochloric acid in one case in which the Ewald meal did cause such secretion, it produced secretion of free hydrochloric acid of a concentration less than that evoked by the Ewald meal in two other cases, and it produced concentration only equal to or within ten points of that evoked by the Ewald stimulus in fourteen cases"

If a fairly uniform response to a given dose of histamine in the same individual at different times could be demonstrated, the method of Bloomfield and Pollard would offer some possibility of a quantitative determination of hydrochloric acid excretion inasmuch as practically all of the secretion over a given period of time is obtained by continuous aspiration This would provide a functional test which could be used in an effort to get some measurable observation in the follow up of chronic gastric cases As yet there is insufficient evidence to show that there is always a constancy of response of volume and of hydrochloric acid secretion to a given amount of histamine in the same individual

Best³ and his associates have found histamine in considerable quantity in many organs the greatest amounts being in the liver, lungs and gastrointestinal tract Ivy⁴ and his co-workers have isolated histamine in crystalline form from the pyloric mucosa of the hog The presence of histamine in so many fresh normal tissues has suggested the possibility of its bearing of physiologic importance, but the presence of more than a lethal dose of histamine in the body points to

strated an inactivating substance which they called histaminase⁵ It is interesting that histamine was not found in the gastric mucosa while a large amount was found in the mucosa of the small and large intestines The fate of histamine in the body is a question of great interest and possibly of considerable physiologic importance

With these recent contributions concerning the gastric physiology we have much information that we do not as yet know how to use, therefore we should be cautious in any dogmatic application in clinical medicine More doubt has been thrown on the diagnostic value of a single gastric analysis by any method, but, also it is demonstrated that in certain instances a single gastric analysis may furnish extremely valuable information when forming a link in the diagnostic chain More adequate quantities of human gastric juice are now available for the study of its known and unknown constituents and information is being provided for the more comprehensive understanding of the relationship of the stomach to the body as a whole

(Contributed editorial by CHARLES L. BROWN, M.D., F.A.C.P., Ann Arbor, Michigan)

¹BLOOMFIELD, A. L., and POLLARD, W. S. The diagnostic value of studies of gastric secretion. *Jr Am Med Assoc*, 1929, xcii, 1508

²COMFORT, M. W., and OSTERBERG, A. E. Gastric secretion after stimulation with histamine in presence of various types of gastric and duodenal lesions, *Jr Am Med Assoc*, 1931, xcvi, 1141

³BEST, C. H., and McHENRY, J. W. The inactivation of histamine. *Jr Phys*, 1930, lxx, 319

⁴SART, J., IVY, A. C., BURGER, J. P., and ALLEN, J. L. Isolation of histamine from the stomach. *Proc Soc Exp Biol Med*, 1931, xxviii, 1141

Abstracts

Analysis of 104 Cases of Carcinoma of the Large Intestine By HOWARD T KARSNER, M D, and BURTON CLARK, JR, M D (Am Jr Cancer, 1932, xvi, 933-970)

In this paper are reported the results of an analysis of 104 cases of proved carcinoma of the large intestine admitted to Lakeside Hospital, Cleveland, in the ten years ending in 1931. Maximum incidence of carcinoma of the colon is found to occur in the fifth and sixth decades of life and to be slightly earlier than for cancer of the rectum. Carcinoma of the colon is distinctly more common in males than in females. Anatomically, cancer is slightly more frequent in the rectum than in the colon. Of cancers of the colon, about one-third are in the sigmoid flexure, one-third in the proximal colon up to and including the hepatic flexure, and the other third in the transverse colon, splenic flexure and descending colon. Widespread metastasis is infrequent. Adenomatous polyps frequently become malignant. Pain is a frequent initial symptom, more especially of cancers of the rectum and sigmoid, but common in the course of the disease in all parts of the colon. Constipation is more notable with cancers of the left half of the colon than with those of the right, but is particularly common with cancers of the three flexures and ascending colon. Vomiting is often recorded with cancers of the splenic and hepatic flexures. Diarrhea is most frequent with the rectal cancers, and the same is true of the alternation of diarrhea and constipation. Blood in the stools is common with rectal cancers and decreases in frequency the higher the site of the cancer in the colon. Obstruction is observed particularly with cancers of the splenic flexure and is next most common with those of the hepatic flexure. Anemia is likely to be more severe in patients with cancer of the right half of the large intestine than in those with the disease

in the left half. Loss of weight is frequent and apparently is more common with cancers of the hepatic flexure, transverse colon, and splenic flexure.

Experimental Transmission of Tularemia by Mosquitoes By CORNELIUS B PHILIP, GORDON E DAVIS, and R R PARKER (Public Health Reports, 1932, xlvii, 2077-2088)

Several cases of human infection with *Bacterium tularensis* are on record in which there has seemed to be good reason to consider mosquitoes as possible vectors. Eight species of mosquitoes were used in a series of experimental investigations of the validity of this assumption. Mechanical transmission was shown to be possible, infection being transferred from infected to healthy guinea pigs by interrupted feeding of *Aedes aegypti* in one instance, and twice by crushing single specimens on the unbroken skin of guinea pigs, 24 hours and 9 days, respectively, after the original infecting feeding by the mosquitoes. Viable organisms were recovered from killed, and also from dead, unincubated *Theobaldia incidens* up to the full life limit of the lot tested, and four days after death. Excrement of *Aedes triseriatus* pressed 24 hours after infecting blood-meals, and of *A. aegypti* 3 and 4 days after such meals was found to be infective. Thus it appears that mosquitoes which had fed on an animal infected with tularemia might infect persons mechanically: (1) by biting after having been interrupted during their meal on the infected animal, (2) by being crushed on the skin with or without subsequent rubbing, and (3) by deposition of excrement on the skin. However, it is likely that suitable conditions to effect such transfers in nature are rare and it is probable that only infrequent infection of man would occur in this manner.

Retrobulbarneuritis durch Apiolvergiftung
[*Retrobulbar Neuritis in the Course of*
"*Apiol*" *Poisoning*] By DR ALEXANDER
JUHÁSZ-SCHÄFFER (Klin Wochenschr,
1932, xi, 1232)

Through reports from Holland, Germany, and Jugoslavia [also South America Editor] a new form of poisoning, "Apiol" poisoning, has been made known. There is a great similarity in the clinical course of the reported cases. Weakness and pain in the extremities, particularly the lower, are followed by varying degrees of paralysis of the involved region. The motor portions of the peripheral nerves are selectively affected. The lack of sensory changes is a point of differential significance in ruling out other forms of polyneuritis. To the case forming the basis of this report special interest attaches since in this patient there developed an acute unilateral retrobulbar neuritis with exophthalmos and limitation of adduction. "Apiol" has a wide reputation among the laity in Europe as an effective and readily obtained abortifacient and it is usually for this purpose that it has been taken in the cases in which poisoning has resulted. Toxic effects apparently depend upon the triorthocresyl phosphate present. [Note identity in clinical course and etiological agent with "jake" poisoning in this country. Editor] The sale of "Apiol" should be restricted or prohibited.

Is the Increase of Cancer Real or Apparent?

By MARGR THURLOW MACKLIN, M.D.
(The Am Jr of Cancer, 1932, xvi, 1193-1205)

"Cancer is increasing, and it is increasing particularly in the age group over sixty. The reason for its increase is not that it is occurring at progressively younger ages, or attacking larger percentages of the younger population. Despite its increase, deaths are fewer from all causes than they were. We have withdrawn from the ravages of infectious disease; we have lost to those diseases which are dependent upon inherent qualities in the chemical and physical makeup of the individual. Cancer is increasing because of progress in medical therapy. There has been a great increase in the use of surgery, of x-rays, and

having grown old, they are kept from dying of those ills from which they formerly suffered. With each increase in the warfare against preventable diseases, there will be an increase in the ravages from cancer, for with each victory is created a greater available population to die from that disease.

"These conclusions are based upon the statistics of Canada. There is strong ground for believing that a similar analysis of the statistics of any other country would lead to the same conclusions. It is true that there may be racial differences in immunity to cancer, but the conclusion here reached will probably prove universal, namely, that excellent public health measures and high cancer rates are inseparable, at least for the present. Those who point to the low cancer rates existing among primitive peoples, and who state that cancer is a disease of modern civilization, neglect to call attention to the fact that preventive medicine is itself a triumph of modern civilization."

The Experimental Intravenous Administration of Colloidal Thorium Dioxide
By DUDLEY A. IRWIN, M.B. (Canada Med Assoc Jr, 1932, xxvii, 130-135)

A 25 per cent colloidal solution of thorium dioxide ("Thorotrast") when injected intravenously into rabbits was found to circulate for about five minutes in the colloidal state and then to flocculate. The flocculated particles were engulfed, for the most part, by the reticulo-endothelium of the liver, spleen, other lymphoid tissues, and bone marrow, and by parenchymatous cells of the liver. Thus fixed in a finely divided state, the thorium dioxide in the liver and spleen produced a shadow permitting the visualization of these organs. The shadow cast by bone marrow was obscured by the covering bone. With large doses the lymphatic glands could be visualized. The presence of thorium dioxide was innocuous in the tissues and no untoward reactions were observed following doses up to 5 cc per kilogram, during a period of four months. During this period there was no evidence of the elimination of the stored thorium dioxide from the spleen, bone marrow, or lymph nodes. In the liver, however, the thorium dioxide gradually ac-

cumulated in the Kupffer cells, which were believed to form emboli in the pulmonary capillaries, thus permitting this portion of the thorium compound to be eliminated in the bronchial mucus

Renal Glycosuria By ALEXANDER MARBLE, M.D. (Am Jr Med Sci, 1932, clxxxiii, 811-831)

Certain standards are set up which constitute a definition of "typical" renal glycosuria. Glycosuria without hyperglycemia must be present and sugar should be found in every specimen of urine examined, whether voided after fasting or after a full meal. The fasting blood sugar value (venous) should not reach nor exceed 0.12 gm per 100 cc, nor after a meal should the value reach or exceed

0.17 gm per 100 cc. Glycosuria should be largely independent of diet and the level of blood sugar should be influenced only slightly by the ingestion of food. The symptomatology characteristic of diabetes mellitus should be absent. The sugar found in the urine should be proved to be dextrose. No progression toward diabetes mellitus should be evident during at least three years of observation. A critical analysis of 9,000 consecutive cases of glycosuria revealed only 15 which met the above tests and which could therefore be considered true examples of renal glycosuria. No evidence of nephritis was found in any of these 15 patients. A history of glycosuria in relatives was obtained in 11. Because of the great rarity of renal glycosuria, care should be taken in making a final diagnosis of this disease.

Reviews

Man and Medicine: An Introduction to Medical Knowledge By DR. HENRY E. SIGERIST, Professor at the University of Leipzig. Introduction by DR. WILLIAM H. WELCH, Professor of the History of Medicine, The Johns Hopkins University. Translated by MARGARET GALT BOISE. x + 340 pages. 1932. W. W. Norton & Company, Inc., New York. Price, \$4.00.

This English version of Sigerist's "Einführung in die Medizin" appears at a most appropriate time, for it has been announced that its distinguished author, who formerly succeeded Sudhoff in Leipzig, has accepted the chair of the history of medicine in The Johns Hopkins University upon the retirement of Dr. Welch. This book presents the history of medicine with a new breadth of vision and by a new method. Under seven major divisions—Man, Sick Man, The Signs of Disease, Disease, Causes of Disease, Medical Aid, and The Physician—is presented all of that mass of intimate knowledge which every man intrinsically craves in respect to the relationship between the human organism and disease processes. This book is

for the physician, it is also for the intelligent layman, and most of all is it for the medical student in the early days of his course. For him it is an experience in orientation in his chosen field. Throughout, the exposition of the knowledge of the present is enriched by abundant references to the past. Dr. Welch writes in the foreword:

"So simple, straightforward and devoid of unnecessary technicalities is the manner of exposition, that interest cannot fail to be aroused by the survey presented in this book of the relation to medical practice of existing knowledge of the structure and functions of the human body in health and in disease, of mental process, of epochal discoveries, of advancement of knowledge by observation and experiment of doctrines held at different times of the origin and nature of disease, of the attitude of society in different ages and countries toward the sick man, of the ideals of the physician and their relation to existing social and cultural conditions in different countries and periods, of the influence of religion and of sports upon the development of hygiene and of the

position of medicine in relation to the life and work of the individual and of society"

The Failing Heart of Middle Life By ALBERT S HYMAN, A B, M D, F A C P, Cardiologist, Beth David and Manhattan General Hospitals, Attending Physician and Cardiologist, Hospital for the Aged, Consulting Cardiologist, Haarlem Day Nursery, Chief Cardiac Clinics, Beth David and Manhattan General Dispensaries, Director, Witkin Foundation for the Study and Prevention of Heart Disease, New York, N Y, and AARON E PARSONNET, M D, C M, F A C P, Attending Physician and Cardiologist, Newark Beth Israel Hospital, Medical Director Home for the Aged, Fellow, Witkin Foundation for the Study and Prevention of Heart Disease, Newark, N J, with a Preface by DAVID RIESMAN, M D, Sc D, F A C P, Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania xx + 538 pages, 160 illustrations and 4 plates F A Davis Company, Philadelphia, 1932 Price, \$5.00 net

The body of this book is divided into six parts, each containing a number of chapters pertaining to its subject matter. Part I deals with the coronary arterial system in health and disease. There is first a brief summary of the blood supply of the heart and then a discussion of the histological structure of the coronary arteries and of the physiologic changes through which they pass. This leads to the subject of coronary sclerosis with its clinical and pathological aspects. The final chapters deal with the various inflammatory lesions of the coronary arteries and the causes and effects of coronary thrombosis. Part II bears the title "The Myocardial Syndrome" and begins with a discussion of the lesions of the heart muscle which may properly be termed myocarditis. This leads to the conditions which the authors prefer to call myocardial infarction to true myocardial infarction. During the course of the book the complete mechanism of the myocardial infarction is described. Part III

is concerned with coronary thrombosis and occlusion. The symptoms of acute coronary thrombosis are described in detail and the important points in differential diagnosis are brought out. Special chapters are devoted to shock and blood pressure changes in this disease. Other chapters deal with the sequelae of coronary thrombosis and the accompanying physical signs. The discussion is then brought to a close by chapters on prognosis and treatment. In Part IV there is given a detailed description of the electrocardiographic findings in the various stages of degenerative heart disease. Over eighty well-chosen electrocardiograms are given to supplement and make clear the text. Part V deals with angina pectoris, discussing the mechanism of the pain production, the cardiac nerve supply and the symptoms of the anginal syndrome. Various theories of etiology are given as are also the immediate and secondary predisposing factors, including the effects of tobacco, alcohol and coffee. The relation of angina pectoris to associated disease conditions and the points of differentiation from coronary thrombosis are emphasized. Finally an excellent presentation of the treatment of this disease, including such recent advances as surgical procedures and the use of tissue extracts, is given. Part VI is devoted to the medicolegal aspects of sudden death from heart disease and in a clear, concise manner cites appropriate cases to illustrate the points made. This is a well written and interesting book which covers the subject adequately. Numerous brief case histories are included and these add to interest and clarity. At the end there is a bibliography of 1250 references rendering complete a work which will be particularly helpful to the general practitioner who has found it difficult to keep up with recent advances in cardiology.

B M H

Diseases of the Kidney By W GIBLING BARR, F R C S (Eng), Surgeon to St Bartholomew's Hospital, London, and GEORGE LAMBS, M D (Cantab), F R C P (Lond), Physician with Charge of Out Patients, St Bartholomew's Hospital, London. 424 pages, 8 colored plates, 152

text-figures P Blakiston's Son & Co, Inc, Philadelphia, 1932 Price, \$7.50

Girling and Ball have endeavored to give an account of kidney disease from the viewpoints of a physician and of a surgeon working in close collaboration. The field to be covered is therefore very broad and herein lies the value of this book. It presents the whole clinical area of pathological conditions of the kidney within a single cover. The first three chapters are devoted to the embryology, anatomy and physiology of the kidney, to a general review of the signs and symptoms of kidney disease and to the technic of examination. Then the various groups of renal lesions are considered. Bright's disease seems to have been put all too severely "in its place" for it, including amyloid disease, is granted but some 74 of the total of over 400 pages. Here the old terminology is followed except for the addition of a section on nephrosis. To many American readers this terminology will be highly confusing. For instance, Acute Interstitial Nephritis is found to refer to the kidney lesions of pyemia with multiple visceral abscesses, while in this country this term is generally accepted as designating the diffuse intertubular inflammatory process typified by postscarlatinal nephritis. This is the least satisfactory section of the book. On the whole, it is clear-cut and accurate in its statements, and the typography and illustrations are excellent. Many of the latter are from gross specimens in the Museum of St Bartholomew's Hospital and are very well chosen. This book can be recommended especially for its presentation of those renal conditions which are of surgical as well as medical import.

The Heart Rate By ERNEST P. BOAS, M.D., Associate Physician, Mt Sinai Hospital, New York City, and ERNST F. GOLDSCHMIDT, Ph.D., Research Fellow (1930-31), Department of Surgery in the Yale University School of Medicine. xi + 166 pages, 68 illustrations, numerous tables. Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland, 1932. Price, \$3.50 postpaid.

In this monograph are presented the data collected during a study of the heart rate by

means of the cardiograph, an electromagnetic device activated by the action currents of the heart. The studies concern healthy subjects under conditions of average activities, patients during anesthesia and operation, and patients under observation for cardiac disability. To the physician accustomed to place considerable weight on the pulse rate, it must come as something of a shock to learn how widely the healthy pulse rate varies under normal conditions even aside from the well known changes of rate induced by physical and emotional stimuli. Valuable clinical information is afforded by the author's studies on subjects during sleep and during anesthesia. The uniform reduction in rate during sleep offers a therapeutic approach in the management of various cardiac disabilities. The acceleration noted during unskillfully administered anesthetics should be unexpected only to the thoughtless. The absence of a significant correlation between body habitus and cardiac rate is surprising. The value of this observation is lessened somewhat by the fact that the morphologic constitutional type was determined by subjective judgment rather than actual measurement. This information would have been more valuable had the individual ages been tabulated in each group. The experiments are evidently carefully conducted and the results are recorded with an eye to detail. This monograph is well written and carries with it a useful and extensive bibliography. It should be available to every worker interested in the fields of cardiology and of metabolism.

H. G.

Practical Treatment of Skin Diseases with Special Reference to Technique By EDWARD AELSHWIDE, M.D., formerly Assistant Physician, University Skin Department, Direction of Prof. Unna, Lippendorf Hospital, Hamburg, Assistant Physician, Clinic and Research Laboratory, Direction of Prof. Unna, Hamburg, Assistant Physician, Institute of Physical Therapy, Direction of O. Ahlswede, M.D., Hamburg. xxvi + 770 pages, 77 illustrations. Paul B. Hoeber, Inc., New York, 1932. Price, \$12.00.

This work differs from all others in the

field of dermatology. It is primarily and almost exclusively concerned with therapy. It not only states clearly what can and should be done for lesions of the skin, but also gives a concise presentation of the technical procedures involved. Naturally, the practices of the Unna school are most fully represented, but there seems to be a fair consideration of the work of others as well. In almost all instances, a sound understanding of the underlying pathology is evident in the brief characterizations of the various affections. However, mycosis fungoides is said to be of unknown etiology and there is no suggestion of the view so generally held in this country that it is a neoplasm of the lymphoblastoma group. Any disappointment felt in this regard is more than offset, however, by the italicized statement that pigmented nevi are best removed surgically with complete excision out of the healthy surrounding tissues and that local treatment of these growths should be avoided, particularly caustics, carbon dioxide snow, and irradiation. To this emphatic pronouncement from a dermatologist, pathologists will give their full approval. This work, with its highly practical arrangement, should prove to be of very great value.

Recent Advances in Pathology. By GEOFFREY HADFIELD, M.D., F.R.C.P. (Lond.), Professor of Pathology in the University of London, Pathologist to the Royal Free Hospital, and LAWRENCE P. GARRON, M.A., M.B., B.Ch. (Camb.), F.R.C.P. (Lond.) Bacteriologist and Lecturer in Bacteriology, Late Demonstrator of Pathology, St. Bartholomew's Hospital. x + 392 pages, 67 illustrations. P. Blakiston's Son & Co., Inc., Philadelphia, 1932. Price, \$3.50 net.

This is a worthwhile member of the Recent Advances Series. While many forward-looking investigations are not mentioned and others have received extensive treatment, many in general the topics presented have been thoroughly and carefully dealt with

Neoplasia as might be expected. The Reticulo-Endothelial System has its chapter, and two are devoted to the Cardio-Vascular System and two to Bright's Disease. The discussion of advances in knowledge of neoplasms is especially well written, while certain other chapters suffer by comparison. The section on Primary Cancer of the Lung is already out-of-date by from three to five years, and the same may be said of the subject matter dealing with the thyroid. The isolation of thyroxin in 1915 is scarcely a 'recent advance', nor should the work of Marine and Manby in 1916 be referred to as a recent study. Nevertheless, this book will prove a useful aid to those whose major textbooks in pathology do not include Asbestosis, Nephrosis, and Oligodendroglioma.

La Distomatosis Hepatica en Cuba [Hepatic Distomatosis in Cuba] By DR PEDRO KOURI and DR ROGELIO ARENAS. 175 pages, numerous illustrations. 1932. Distributed by the authors, Neptuno 115, Havana, Cuba.

This monograph is made up of reprinted articles from "Vida Nueva" with certain added material. The first section gives a detailed account of two human cases of hepatic distomatosis produced by *Fasciola hepatica*. In the second the occurrence of this condition in Cuba is surveyed and treatment is discussed, while in the third the specific action of emetine is emphasized.

Methodenlehre der therapeutischen Untersuchung [Methodology in Therapeutic Investigation] Von PAUL MARTINI, Professor der Medizin, Direktor der medizinischen Klinik der Universität Bonn. 69 pages, 9 illustrations. Verlag von Julius Springer, Berlin, 1932. Price, in paper, RM \$1.50.

This monograph presents a philosophical introduction to the theory of therapeutic investigation. Emphasis is placed upon mathematical analysis of apparent results in treatment and their evaluation.

College News Notes

The plan of assembling a library of all books published by members of the American College of Physicians was initiated about four years ago. Although much progress has been made through the receipt of gifts of books from members, there are a number of members who have not yet contributed books of which they are authors. This library will have a growing interest and value as years go by, for it is intended to be a memorial of our members.

The most recent contribution to the library has been made by Dr John H Musser (Fellow), New Orleans, La., editor of a new book entitled "Internal Medicine—Its Theory and Practice", published by Lea & Febiger, Philadelphia (1932). The book contains 1316 pages, consisting of twenty-seven chapters—each chapter contributed by a different individual, holding a professorial appointment in a medical school and selected because of particular interest in, and knowledge of, the subject of which he has written. Among the twenty-seven authors appear the following physicians who are Fellows of the American College of Physicians:

David P Barr, St Louis
 Arthur L Bloomfield, San Francisco
 George E Brown, Rochester, Minn
 Robert A Cooke, New York
 Charles F Craig, New Orleans
 Ralph A Kinsella, St Louis
 Edward B Krumbhaar, Philadelphia
 Isaac Ivan Lemann, New Orleans
 William Sharp McCann, Rochester, N Y
 James H Means, Boston
 James Alex Miller, New York
 John H Musser, New Orleans
 O H Perry Pepper, Philadelphia
 Maurice C Pincoffs, Baltimore
 Fred M Smith, Iowa City
 Edward A Strecker, Philadelphia
 Cyrus C Sturgis, Ann Arbor
 Virgil Preston Sidensticker, Augusta
 Robert Grant Torrey, Philadelphia

Robert Van Valzah, Madison, Wis

The following additional physicians, not Fellows of the College, are also contributors:

Marion Arthur Blankenhorn, Cleveland
 Alan M Chesney, Baltimore
 Ernest Carroll Faust, New Orleans
 A Graeme Mitchell, Cincinnati
 Hobart A Reimann, Minneapolis
 Russell M Wilder, Rochester, Minn
 George Wilson, Philadelphia

President F M Pottenger has appointed the following standing Committee on ANNALS OF INTERNAL MEDICINE to have advisory supervision of the Journal:

Dr James H Means, Boston
 Dr O H Perry Pepper, Philadelphia
 Dr David P Barr, St Louis
 Ex-officio

The Editor

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr Frederick R Barnes (Fellow), Fall River, Mass.—2 reprints,
 Dr Archie A Barron (Fellow), Charlotte, N C—1 reprint,
 Dr Moses Barron (Fellow), Minneapolis, Minn—21 reprints,
 Dr Wm R Brooksher, Jr (Fellow), Fort Smith, Ark.—7 reprints
 Dr Harold C Denman (Fellow), Brooklyn, N Y—1 reprint,
 Dr John A Hooke (Associate), Detroit, Mich.—1 reprint,
 Dr George L Steck (Fellow), Springfield, Mass.—1 reprint,
 Dr Martin J Symott (Fellow), Montclair, N J—1 reprint,
 Dr Pauline Williams (Fellow), Richmond, Va.—1 reprint
 Dr Philip Worl (Fellow), Denver, Colo.—7 reprints

Dr Albert F. R. Andresen (Fellow), Brooklyn, Dr. Henry L. Bockus (Fellow), Philadelphia, and Dr George B. Eusterman (Fellow), Rochester, Minn., are Vice-Chairman, Secretary and member of the Executive Committee, respectively, of the Section on Gastro-enterology and Proctology of the American Medical Association

Dr William S. Hubbard (Fellow), Chief of the Medical Service, St John's Hospital, Brooklyn, has retired (age limit) to the emeritus rank

Dr Irving Gray (Fellow), Brooklyn, is Chairman of the Scientific Section of the Second District Branch of the New York State Medical Society

Dr J. Burns Amberson (Fellow), New York City, attended the International Union Meeting at The Hague during September

Dr Henry C. Sweany (Fellow), Chicago, has been elected President of the Mississippi Valley Sanatorium Association

Dr Ernest S. Mariette (Fellow), Oak Terrace Minn., has been elected President of the Mississippi Valley Conference on Tuberculosis

Dr Gerald B. Webb (Fellow), Colorado Springs, has been named President-Elect of the Colorado State Medical Society

Under the Presidency of Dr L. J. Moorhead (Fellow), Oklahoma City, the Southern Medical Association held its annual meeting in Birmingham, Ala., November 16 to 18

The sixty-ninth session of the Homeopathic Medical Society of the State of Pennsylvania was held at Sky Top Lodge, Monroe County, Pa., September 27, 28 and 29. The following members participated as invited guests:

Dr Carl V. Vreener (Fellow), Philadelphia, President of the Bureau of Homeopathic Medicine.

Dr D. J. P. Fennell (Fellow), Philadelphia, presented a paper on "The Application

of an Isopathic Treatment to a Case of Sulpharsphenamine Poisoning as recommended by Richter",

Dr E. Roland Snader, Jr (Fellow), Philadelphia, presented a paper on "Unusual Laboratory Findings in Diabetes Mellitus",

Dr Ralph Bernstein (Fellow), Philadelphia, presented a paper on "Dermatologic Aphorisms",

Dr Carl V. Vischer (Fellow) and Dr Lowell L. Lane (Associate), both of Philadelphia, presented a paper on "A Clinical Consideration of the Paroxysmal Tachycardias",

Dr G. Harlan Wells (Fellow), Philadelphia, discussed a paper by Dr Clarence Bartlett, "Fallacies and Traditions in Medicine",

Dr Dunne W. Kirby (Associate), Philadelphia, discussed the paper mentioned above by Dr Ferguson,

Dr Grant O. Favorite (Associate), Philadelphia, presented a paper on "Infectious Mononucleosis—Case Report",

Dr Samuel W. Sappington (Fellow) and Dr Grant O. Favorite (Associate), both of Philadelphia, had charge of the Scientific Exhibits A—Heart Pathology, B—Tumors of the Large Intestine,

Dr William Devitt (Fellow), Allenwood, Pa., was the guest speaker of the Bureau of Clinical Medicine

Dr Frank N. Allan (Fellow), who has been Associate in Medicine at the Mayo Clinic, Rochester, Minn., and Instructor in Medicine at the University of Minnesota (Mayo Foundation), has resigned to accept a position with the Lahey Clinic, Boston, Mass.

Dr Egerton Crispin (Fellow), Los Angeles, Calif., President of the Resident and Ex-Resident's Association of the Mayo Clinic and the Mayo Foundation, delivered the presidential address at the annual meeting, October 13, 14 and 15, at Rochester, Minn., on "Chance Factors in Medicine".

Dr William C. Moorhead (Fellow), San Francisco, addressed the annual meeting of the National Health Officer Association

at San Diego, September 26 on "Trends in the Control of Tuberculosis", and on October 11 spoke before the monthly meeting of the Santa Cruz Medical Society on "Pulmonary Conditions Wrongly Diagnosed as Tuberculosis"

Dr E J G Beardslev (Fellow), Philadelphia, addressed "The Porch Club" of Riverton, N J, October 4, on "The Search for Health and Happiness as a Physician Views It"

Dr Beardslev was a guest speaker of the West Jersey Homeopathic Medical Society at its meeting at the Tavestock Country Club, Haddonfield, N J, October 14, his subject being "Complete Routine Physical Examinations vs Intuitive Diagnoses"

The Inter-State Postgraduate Medical Association of North America held its annual Assembly at Indianapolis October 24-28, under the Presidency of Dr Arthur D Bevan, of Chicago. The following Fellows of the College contributed to the program as indicated

Dr O H Perry Pepper, Philadelphia—Diagnostic Clinic and "Comments on the Group of Diseases Attributed to Filterable Viruses",

Dr Elsworth S Smith, St Louis—Diagnostic Clinic and "Prognosis and Treatment of Ambulatory Cases Presenting the Angioid Syndrome",

Dr David P Barr, St Louis—Diagnostic Clinic and "The Effects of Diseases of the Thyroid Gland on the Heart",

Dr Lewellys F Barker, Baltimore Md—Diagnostic Clinic and "The Senile Patient";

Dr Warfield T Longcope, Baltimore—Diagnostic Clinic and "Constipation"

Dr Cyrus C Sturgis, Ann Arbor, Mich—Diagnostic Clinic and "Pernicious Anemia",

Dr W McKim Marriott, St Louis—Diagnostic Clinic (Pediatrics) and "Polioviruses",

Dr Charles A Elliott, Chicago—Diagnostic Clinic and "The Leukemias—Their Significance and Their Treatment",

Dr Emanuel Libman, New York City—

Diagnostic Clinic and "Immediate and Ultimate Prognosis in Cardiac Disease",

Dr Henry A Christian, Boston—Diagnostic Clinic and "Pharmacological Action of Digitalis",

Dr Elliott P Joslin, Boston—Diagnostic Clinic and "The Present Status of the Diabetic Child",

Dr Harlow Brooks, New York City—Diagnostic Clinic and "Essential Hypertension—Its Implications and Treatment"

Dr Willis F Manges (Fellow) Philadelphia, delivered an address on "The Development of Roentgenology", at the opening of Jefferson Medical College of Philadelphia on September 21

Dr Ross V Patterson (Fellow), dean of the Jefferson Medical College, announced the appointments to the staff of Dr Henry K Mohler (Fellow), Philadelphia, and Dr Harold W Jones (Fellow), Philadelphia as Associate Professors of Medicine

Dr Frieda Baumann (Fellow), Philadelphia, has been promoted to Associate Professor of Applied Therapeutics in the Woman's Medical College of Pennsylvania

Dr W H Stoner (Fellow), formerly Medical Director of Hoffmann-La Roche Inc Nutley N J is now attached as Research Consultant to the Experimental Research Laboratories of Burroughs Wellcome & Company, at Tuckahoe N Y. He will visit institutions in the United States and Canada in which research of medical significance is conducted, and will then publish a report of the survey for the aid of research workers in avoiding duplication of effort, and in establishing contacts between workers in similar fields

Dr Salvatore Toracomo (Fellow) Marquette, Mich, has been elected President of the Michigan Sanatorium Association

Dr Samuel Goldberg (Associate), Philadelphia has been appointed to the staff of the Department of Pediatrics of Temple

University School of Medicine A sixty-bed addition to the building of the Department has been begun

Dr Edward Weiss (Fellow), Philadelphia, has been appointed as Clinical Professor of Medicine, and Dr Joseph C Doane (Fellow), Philadelphia, has been promoted to Clinical Professor of Medicine in the Department of Medicine at the above institution

Dr Clyde Brooks (Fellow), formerly Professor of Physiology and Pharmacology at the University of Alabama School of Medicine, has been appointed to the staff of

the Louisiana State University Medical Center, New Orleans, as Professor of Physiology

Dr Augustus Warren Crane (Fellow), Kalamazoo, Mich, was the recipient of the honorary degree of Master of Arts from the University of Michigan on the occasion of its 83rd Annual Founder's Day Ceremony at the Medical School on September 26 The address by Dr Crane on that occasion dealt with development of knowledge of magnetic and electrical phenomena leading up to the work of Roentgen

OBITUARIES

DOCTOR RAY CARRINGTON BLANKINSHIP

Dr Ray Carrington Blankinship (Fellow), Madison, Wisconsin, died suddenly of coronary thrombosis at Huntington, West Virginia, August 23, 1932

Dr Blankinship was born at Brookneal, Virginia, July 31, 1890 He obtained his undergraduate education at Virginia Polytechnic Institute and his medical education at the Medical College of Virginia, at which institution he received the degree of Doctor of Medicine in 1914 He served an eighteen months' internship at Kings County Hospital, Brooklyn, N. Y. and then returned to Virginia to practice medicine at Marion. In December of 1917 he was commissioned a lieutenant in the Medical Corps of the United States Army and was sent to Camp Travis, San Antonio, Texas, where he remained until March, 1919

In 1917 he married Eleanor Adelaide Stone of Stoughton, Wisconsin and

upon leaving the Army, he returned to civil practice at Stoughton From there he moved to Madison to join the staff of the University of Wisconsin Student Health Service He later specialized in gastro-intestinal diseases, and upon the establishment of the four year course in medicine at the University of Wisconsin in 1925, he became chief of the division of gastro-enterology, as Associate Professor of Clinical Medicine This position he held at the time of his death

Dr Blankinship was a member of the Wisconsin State Medical Association, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1922

The following is quoted as a part of a resolution adopted by the faculty of the University of Wisconsin Medical School:

"The rare characteristics of humanist and scientist combined in him the best of the old family doctor and the new scientific physician He knew both

the art and science of medicine His interest in people made him acutely sensitive to that relation of physician to patient which cannot be reached by science His patients, recognizing in him the artful practice of scientific medicine, were obedient to his orders and became his life long friends "

(Furnished by J S EVANS, M D , F A C P , Madison, Wis)

DOCTOR LUTHER C DAVIS

Dr Luther C Davis was born in Fairmont, West Virginia, 1894, where he made his preliminary preparation for medicine He was matriculated in the University of Wisconsin, and later entered the University of Missouri where he took his A B degree in 1916 His first intention was to be a chemist but he changed to be a physician, entering the University of Pennsylvania where he was awarded his M D degree, 1920 He served an internship and returned to Fairmont to practice

Dr Davis was an outstanding man in his profession, very scientific, he was the possessor of one of the first electrocardiographs in the State He contributed a number of scientific papers on diseases of the heart, was an untiring member of the State Medical Association, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1926

Dr Davis had one of the largest practices in Fairmont, and was a consultant with patients from a large part of the State His skill, sympathy and charming personality endeared him to

his clientele and to his professional brethren

His death, due to an automobile accident near Coleville, California, while returning with a companion from a fishing trip has brought great sorrow to his friends and to the profession of the State

(Furnished by JOHN N SIMPSON M D , F A C P , Governor for West Virginia)

DOCTOR LORRAINE SCHWARTZ

Dr Lorraine Schwartz (Fellow), of Pittsburgh, Pa , died July 25, 1932, from brain injury resulting from a fall

Dr Schwartz was born in Slainesville, West Virginia, February 9, 1874 He attended Jefferson Medical College of Philadelphia, graduating in 1903 During 1903-04 he was an intern at the Mercy Hospital of Pittsburgh and to the time of his death was on the staff of that hospital His list of appointments included Dermatologist and Syphilographer, Mercy Hospital, Columbia Hospital and Rosalia Foundling Asylum Dr Schwartz was a member of the Allegheny County Medical Society, a member of the Pennsylvania State Medical Society, a member of the American Therapeutic Society, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians (since 1920)

June 7, 1906, Dr Schwartz was married to Miss Maud Bishoff of Pittsburgh who survives him

Dr Schwartz was a Mason, a member of the University Club and of the

Pittsburgh Country Club. He was a member of the Third Presbyterian Church of Pittsburgh.

For several years before his death Dr. Schwartz had been in poor health and, during this period, traveled extensively in this country and abroad.

A genial companion and a prac-

itioner of outstanding ability in his chosen field, Dr. Schwartz is greatly missed by a wide circle of friends both within the medical profession and without.

(Furnished by E. BOSWORTH MCCREADY, M.D., F.A.C.P., Governor for Western Pennsylvania.)

The December Issue of the Annals of Internal Medicine

- The Manner of Onset in Acute Rheumatic Fever as Seen in New York City
HARLOW BROOKS and CHARLES O'REGAN
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- Insulin in Malnutrition Further Observations (1) ROY D. METZ
- Carotinemia Associated with the Ingestion of Pumpkin Report of a Case
A. C. CURTIS and E. E. KLEINSCHMIDT
- A Comparison of Blood Pressure in Men and Women, a Statistical Study of 3540 Individuals
MACNIDER WITHERBY
- The Action of Benzol, Roentgen-Rays and Radium on the Blood and Blood-Forming Organs
EDWIN F. OSGOOD
- A Further Study of a White Family Showing Elliptical Erythrocytes WARREN C. HUNTER
- Potassium Sulphocyanate A Note on its Use for the Painful Crises in Sickle Cell Anemia
EDWARD C. TORRANCE and TRUMAN C. SCHNABEL
- An Assay of Goldenrod as a Cause of Hay Fever
WARREN T. VAUGHAN and RUTH W. CROCKITT
- The Present Status of the Ketogenic Diet D. SCHUYLER PUTTEND
- The Treatment of Cavities in Pulmonary Tuberculosis LEROY S. PETERS
- Chronic Invalidism with Marked Personality Changes due to Moxedem
HENRY B. STOFF
- Medical and Medical Center MAURICE F. ADAMS

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The Manner of Onset in Acute Rheumatic Fever As Seen in New York City

By HARLOW BROOKS, M S , M D , F A C P , and CHARLES O'REGAN, B A , M D ,
New York City

IT IS universally recognized that rheumatic fever differs materially in its rate of occurrence, in its clinical picture and even in its complications in various parts of the world. Even with very slight variance in geographical distribution, the disease is strikingly modified in many of its most essential respects. Longcope has several times called attention to the fact that the disease as it appears at even so short a distance from New York as Baltimore is very different both in occurrence and in symptomatology. Rare in the tropics, and even in the subtropics, the disease is hardly recognizable to the student familiar with its picture as it occurs in the North.

Altitude and barometric conditions in general also profoundly alter almost all the evidences of the disease. Its seasonable appearance, its relationship to weather conditions and even to in-

dustrial states are still other evidences that factors beyond any single specific agent must be vitally concerned in its production. Familial occurrence and the evident rôle which allergic states play in the disease are still other indications that factors in addition to a single specific infectious agent must be concerned in the development of the condition. It seems very probable, indeed, that the reactions of the patient to the infection are more determinative in this disease than the characteristics of the essential infectious agent.

No experienced clinician, however, can now justify the older assumptions that the disease had essentially to do with disturbances of metabolism, or of diet, for all the clinical manifestations distinctly class the disease as a specific one and as one due to some transmissible infection, even though as yet little unanimity of opinion exists as to just what this specific organism may be. One must therefore be careful in respect to recognizing as specifically

From the Fourth Medical Service of Bellevue Hospital, and The Nursery and Child's Hospital, New York City

essential, organisms which may in truth be but associated biological factors, several of which we know to exist with great frequency in this disease.

Still other confusing factors are those of the rôles played by traumatism, exhaustion, exposure and of familial occurrence, all of which are too frequently seen as determinative or modifying factors in the disease to be dismissed by the student as mere coincidences

Notwithstanding the preeminence which the study of etiology has recently taken in this great problem, the clinical aspects still present much that requires further observation, study and conclusion

At the outset it must be recognized, that as before stated, the disease presents a character apparently determined in large part by locality and hence the description of any phases of occurrence will not apply to the problem as it appears universally

The disease is exceedingly frequent in and about New York City. Five hundred consecutive typical instances were selected from the records of the Fourth Medical Service of Bellevue Hospital as occurring within the past four years. This service represents but one-fourth of the census of the medical divisions of Bellevue, hence it can be seen how very common the disease is in this city. It is believed that the diagnosis of rheumatic fever is correct in each instance included in this series since all questionable cases were eliminated from our statistics.

It is believed by many that social conditions greatly influence the occurrence and character of rheumatic fever.

It is believed by many that social conditions greatly influence the occurrence and character of rheumatic fever. servers to be true of the infection as it occurs in New York City, though the questions of exhaustion and exposure and especially of weather, profoundly influence the cases which appear in this city. Nonetheless, so that we might, in so far as possible, avoid criticism on this score, our series of 700 cases has been consecutively selected, 500 cases from the Fourth Medical Service of Bellevue Hospital, which is our largest city hospital, devoted entirely to the service of the poor; and 150 consecutive cases have been taken from the private and consultation practice of one of us. Since infants are not regularly included on the medical service at Bellevue 50 cases have been taken from the records of the Nursery and Child's Hospital, with the permission and through the great courtesy of Doctor Schloss, Director of the Pediatric division of that hospital.

This present study covers only the problem of the manner of onset in rheumatic fever as it occurs in New York City. For obvious reasons many other phases of the problem are reserved for later presentation, for it is felt that only thus could we properly present the large and constantly increasing material at our command.

It is the belief of the authors that chorea represents but a special clinical picture of rheumatic infection, hence in this group of 50 cases taken from the records of the Nursery and Child's Hospital, but 22 cases were filed under the diagnosis of rheumatic fever and 28 instances were catalogued as chorea. All of the remaining cases were typical examples of rheumatic fever as seen in New York City. In 450

but a good many of these cases subsequently returned to the service with reinfections

SEX

Sex is believed by some to be a matter of importance in the occurrence of rheumatic fever. It is the opinion of the authors that this is true only because males are as a class more frequently exposed to the conditions which we believe to invite the infection. Particularly in this regard must one consider hard physical labor and exposure to adverse weather conditions, also the important factor of physical exhaustion. It is also probable that a greater degree of dissipation and self neglect on the part of the males in general may be a factor in this respect. Our statistics, however, show about the usual incidence in respect to sex, with 443 males and 257 females.

AGE

As in most other localities where rheumatic fever occurs frequently, the preponderance of cases appears at that period of life which demands the greatest physical activity, but they show also a relatively high percentage of occurrence in infantile life, when one takes into consideration the relatively smaller group from this service. The figures are as follows: First decade, 50 cases, second decade, 140, third, 210, fourth, 171, fifth, 88 cases, sixth decade, 26, seventh, 9, and the eighth decade, 6 cases.

FIRST SYMPTOM

Catarrhal inflammatory processes of the upper respiratory tract are pre-

ponderatingly the most frequent and usually the very earliest indication of the infection. Unlike the nasopharyngitis of the "common cold" as studied by most recent investigators, that of the onset of rheumatic fever as it occurs in New York is almost invariably accompanied by fever, often a very high one. No sharp differentiation is of course possible between nasopharyngitis and involvement of the adjacent cavities, but in 347 cases this condition was cited as a pharyngitis. This high rate was even exceeded by the diagnosis of tonsillitis, which was recorded 382 times. Simple "sore throat" was cited by 124 patients without specification of the precise lesion which was present. In 33 instances a paranasal sinusitis was diagnosed by the medical (not the special) staff. It is notable that the cases presenting medically recognizable sinusitis were particularly virulent and rapid cases.

ADENITIS

The very early appearance of adenitis in many cases was one of the surprises of our study. This lesion was strikingly present in 187 instances. Although most frequent in the lymph nodes of the neck, particularly in the tonsillar lymph nodes at the angle of the inferior maxilla, it was often widespread and it was found frequently antedating joint invasion in the groups of nodes draining from the involved extremities. In a few cases the adenitis was of rapid development and so pronounced that acute lymphatic leukemia was considered. Several of these cases showed in addition a most puzzling lymphocytosis but in the average instance at onset but a low grade

polynuclear leucocytosis was found. Streptococci were isolated from such nodes in several instances

FEVER

Fever was present in all cases at some early period of the onset. Occasionally it was very high, but usually not. It was accompanied by a proportionately increased pulse rate except when early cardiac involvement had taken place in which case the heart rate corresponded to, and was indicative of the cardiac process.

CHILL

Chill was infrequently seen or complained of during the period of onset as we have studied it. It was noted but 65 times and then chiefly as a patient's complaint. It occurred more frequently, however, later in the disease, particularly with the development of deep complications or in phlebitis. It has, however, never been an important evidence of the disease as we have seen it.

SWEATING

Sweating, which subsequently often becomes one of the most striking and annoying symptoms of the disease, is not so very common in the period of onset and it is rarely complained of by our patients, possibly because of more distressing symptoms which are present at this time.

EVIDENCES OF OCCULT INFECTION

In view of the present, perhaps excessive interest in this possibility of origin, it may be pointed out that tonsillitis was noted in 382 cases as already mentioned. It is well recognized

that such a general infection might also originate from the nasopharyngitis and sinusitis which are so very frequent, also, in the onset of this disease.

DENTAL INFECTION

The possibility of infection from bad or infected teeth must be admitted in 238 instances. All cases are included in this group in which this possibility had been sufficiently considered to bring about extractions for this cause, or in which a well established dental infection was recognized as a result of study of X-ray plates taken, or of cultures made from extracted teeth. This high occurrence of infected teeth must, however, be considered in association with the fact that in Bellevue Hospital probably an equally high percentage of bad dental status would be found in association with almost any other condition, traumatic, accidental or otherwise. It must be, however, pointed out that of the fifty instances from the Nursery and Child's Hospital, bad teeth, possibly infected, were noted in 16.

ARTHRITIS

Arthritis is the most constant outstanding diagnostic index of this disease as it appears in New York City. It was present in the period of onset or very shortly thereafter in 622 of our cases. Occasionally it is the very first indication of disease noted by the patient. In the patients admitted to the Bellevue service it was present in greater or lesser degree in every instance at the time that they sought admission to the hospital. It occasionally becomes definite before pharyn-

gitis or tonsillitis is discovered. It is distinctly migratory in type and there are few exceptions to the rule of polyarthritis. Monoarticular cases are very rare or entirely wanting as the disease of rheumatic fever occurs in New York City. Exceptions to this rule usually imply mistaken diagnosis with confusion, for example, with gonococcal or septic arthritis.

The clinical picture of the joint lesion need not be detailed here since it is familiar from text book descriptions. It is essentially a peri-arthritis, the large joints are most frequently involved, but by no means exclusively so. Occasionally there is a considerable effusion into the joint space itself, but this is not the usual thing. The synovial membranes are rarely eroded in the acute phases of the disease. Various microorganisms are frequently detectable in the joint fluid. Streptococci preponderate in most instances, but the authors do not as yet accept any of the organisms described as of proven etiological significance.

Sixty-two cases from the Bellevue series, were complicated by certain or possible gonococcal infection. The arthritis in such cases, especially at onset, is usually somewhat atypical. The two forms of arthritis may unquestionably be associated in the same case. Nineteen of the Bellevue cases occurred in the presence of chronic syphilis. This also causes a modification of the joint lesions in some but not all instances.

As a rule, with exceptions, when the arthritis attacks a previously involved joint, the older ones subside somewhat in activity but reinfection frequently follows. An increase in the

temperature commonly immediately precedes invasion of a new joint. The leucocytosis is not much altered as a rule, when migration takes place.

CARDIAC DISEASE

Of the total of 700 cases, 154 entered with initial complaints explainable only on the basis of cardiac disease, apparently caused by the rheumatic fever. Four hundred and ninety-three cases showed at their first examination definite cardiac disease believed to be rheumatic and detectable by the ordinary methods of physical examination. From our subsequent experience with the electrocardiograph we believe that practically all instances of acute rheumatic fever present evidences, electrocardiographic or gross, of cardiac involvement. Certain cases may recover sufficiently, under proper control and treatment, so that some of these lesions may entirely disappear. Even mitral endocarditis of rheumatic origin apparently may heal in children so that the lesion may not be detectable in after life, but these cases are rare. Our studies of the period of onset indicate that cardiac lesions appear in the disease seen in New York City very early in the infection.

Six hundred and six cases were ultimately discharged with clinically recognizable rheumatic cardiac disease. We know from follow up observation that a good many of the apparently free instances at the time of discharge subsequently developed gross cardiac disease, presumably attributable to the initial attack of rheumatic fever. Such lesions apparently may first appear weeks, months and perhaps years after the initial cardiac defect which may

occur without recognition by the usual method of observation. We thus corroborate the observations of Swift in this respect.

PULMONARY, BRONCHIAL AND PLEURAL DISEASE

Sixty-three cases entered with signs or symptoms of tracheitis, bronchitis, pulmonitis or pleurisy. Pulmonary pathology certainly develops in a much higher percentage of New York City cases than the usual text book description implies. As a rule even the type of frank broncho-pneumonia which develops in the course of rheumatic fever runs a rather milder course. Initial rheumatic pneumonia is often present but the clinical course of these cases appears more mild than in a similar degree of ordinary pulmonary disease, independent of rheumatism. Further study of these cases is certainly advisable before any sweeping conclusions be drawn either as to their course or pathology.

EVIDENCES OF ALLERGY

In 42 instances skin lesions, suggestive of allergic disorders, appeared early after onset. None of these seemed to have been excited by drug action, but we cannot be certain on this point. A history of familial or personal asthma was obtained with some frequency. We are as yet unwilling to admit its definite relation to rheumatic fever, however.

SUMMARY

Rheumatic fever is very frequent in New York City.

In the groups studied, it appears more frequently in the male

It is seen most commonly in the second, third and fourth decades, but may occur at any period of life.

Primary attacks are more frequent in this present series, but recurrence of the disease is probably the rule.

The most frequent prodromal or initial symptoms are tonsillitis, pharyngitis, simple sore throat or sinus infections; in short, a catarrhal disease of the upper respiratory passages. Sinusitis, while infrequently diagnosed on medical services, is probably very frequent.

Adenitis, not only of the cervical but also of other systems is a frequent introductory sign. It is of persistent character and prone to reactivation.

Initial symptoms of pulmonary involvement are not dominant in this group of cases. Pulmonary involvement is, however, probably more frequent and important later in the disease than is commonly recognized.

Occult infection, if introductory of the disease, may occur from the nasopharynx and the accessory sinuses, from the tonsil or possibly from dental infection. Infection from the tonsils or from the nasopharynx seems more definitely indicated by these studies.

There are some early indications of possibly allergic character, but they are not common in this group.

Fever is an early and constant symptom. Chill is not frequent. Sweating is not striking in the period of onset.

Arthritis is almost constant and is highly characteristic. It occurs early and as part of the onset. It is distinctly a polyarthritis and of a migratory character, highly diagnostic in appearance and course.

Cardiac involvement is exceedingly frequent, perhaps constant. It occurs early in onset. Few cases escape eventual cardiac invasion of some degree.

Involvement of the nervous system is very rare in the period of onset. Delirium is exceedingly infrequent.

Renal symptoms are very rare in

the period of onset, and subsequently

CONCLUSION

The onset of rheumatic fever, as it occurs in New York City, is highly characteristic and easily diagnosed as a rule. It is almost always associated with early cardiac involvement and a very characteristic type of arthritis.

An Introduction to Medicine

“**T**O the student the value of a persistent endeavor to correlate symptoms with lesions lies not so much in the number of facts which he may succeed in memorizing, as in the development of an attitude of mind which may color the whole of his future professional career. The clinical-pathological conference owes its popularity to the realization of this fact. Education can achieve no higher success than by leaving its abiding imprint on the mental outlook of those who come under its influence.

“To the clinician who wishes to indulge in the periodic brain-dusting recommended by Osler there are few more valuable correctives than a renewed acquaintance with the facts of morbid anatomy as revealed in the postmortem room. It is more than one hundred and thirty years since Bichat wrote the following words, but they are as true today as they were then: ‘You may take notes for twenty years from morning to night at the bedside of the sick upon the diseases of the heart, the lungs, the gastric viscera, etc., and all will be to you only a confusion of symptoms which, not being united in one point, will necessarily present only a train of incoherent phenomena. Open a few bodies and this obscurity will soon disappear, which observation alone would never have been able to have dissipated. Dissect in anatomy, experiment in physiology, follow the disease and make the autopsy in medicine. This is the three-fold path without which there can be no anatomist, no physiologist, no physician.’”

(From *A Text-Book of Pathology: An Introduction to Medicine* by WILLIAM BOYD, Lea & Febiger, Philadelphia, 1932. See review in this issue.)

Observations on Obesity

By RUSSELL M. WILDER, M.D., *Rochester, Minnesota*, and FLORENCE H. SMITH, B.S. and IRENE SANDIFORD, Ph.D., *Chicago, Illinois*

IT IS repeatedly affirmed that certain men and women maintain themselves in weight equilibrium or even gain weight on less food than others require, and popular opinion attributes this to abnormalities of endocrine activity and resulting economies in energy production. It has been repeatedly demonstrated that the basal metabolic rate, measured in terms of calories of heat production for each square meter of surface area, is normal in obesity and that no economy of energy exchange is accomplished in this particular, but the total energy exchange is the crux of the matter, and whether economies can be expected in total metabolism from pituitary, gonadal or other influences, is still open to discussion.

The direct measurement of total metabolism involves an elaborate experimental machinery, a calorimeter large enough to permit the subject to lead a life with a normal amount, or at least some standardized amount, of physical exertion. It also demands several trained technicians to conduct uninterruptedly the necessarily large

number of gaseous and other analyses of consecutive twenty-four-hour periods. Relatively few experiments of this kind have been attempted and none has been entirely satisfactory. Indirect measurements of energy exchange which depend on estimations of amounts of food consumed are exposed to errors introduced by the questionable honesty of many subjects. They are also influenced by fluctuations of water balance, especially significant in obesity, and measurements of water balance involve very particular difficulties. A study of the total water exchange by Newburgh and his associates in connection with a study of the total metabolism in obesity revealed how completely the retention of water may mask the actual loss of tissue occasioned by submaintenance diets. The body weights of Newburgh's subjects inevitably fell to the values anticipated from the metabolic data, but periods intervened when the weights were stationary. The longest of these periods was sixteen days.

NEGATIVE PHASE OF METABOLISM

Our interest in obesity was renewed by the demonstration of Lauter and of Bernhardt of "negative phase" of metabolism occurring after the ingestion of food and after short periods

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of light muscular exercise Strang and McClugage have reinvestigated the heat production following the ingestion of food in normal, obese and thin subjects They were unable to demonstrate a consistent occurrence of a negative phase after a test meal, and they showed that whenever decreases in heat production occurred there was an abnormal elevation of the basal heat production This is, of course, in agreement with the early work of Benedict and Carpenter who not only pointed out the extreme importance of an accurate base line in such experiments but also demonstrated that a negative phase was not encountered after ingestion of food by normal subjects

It has been established that obese subjects expend at least as much and usually more energy for measured amounts of work than is demanded of individuals of normal weight, but Bernhardt, in cases of certain types of obesity and in cases in which individuals were regaining weight previously lost, was led to believe that the rate of heat production would fall immediately after the performance of light work to a level which was lower than the resting or basal level and remain below this level for a time sufficient to compensate for the extra energy expended in the work (figure 1) Here indeed was an economy which might permit an individual to hold his weight or gain on a food allowance smaller than that required for a total metabolism based on conventional calculations, and in fact Bernhardt reported that his subjects gained weight on diets designed to meet, but not exceed, their twenty-four-hour

basal metabolism, although they were up and about and thus expending "extra" energy for work

We have attempted to duplicate these observations, and our data are presented in tables I and II, and partly in figure 2 Our subjects were adults one man and six women One patient had anorexia nervosa (case 6) and was gaining weight rapidly, the others were in varying states of obesity In cases 1, 2, and 3 the patients had been hospitalized for several weeks, they were on basal calorie diets and were losing in weight at the time of the work tests In cases 4, 5, and 7 the patients were hospitalized approximately one week before the work tests were made and at the time of admission were gaining in weight

For the determination of the metabolic rates the gasometer method with analysis of the expired air in the Haldane analysis apparatus was used The details of the technic have been published by one of us elsewhere⁷ In order to insure as accurate results as possible each patient had several metabolism tests as preliminary training before the work tests were done, and from the satisfactory values an average base line was obtained which served as a check on the basal calories obtained on the day of the work experiments The subjects were fasting from the previous evening's meal and were afebrile They rested quietly in bed for at least half an hour before the basal calories each hour were determined in duplicate tests The patients in cases 1 and 2 had had numerous determinations of metabolic rate and apparently they were quite undisturbed by the procedures, there-

fore occasionally the basal calories each hour were determined only once. As can be seen from table 1 this was not satisfactory and later duplicate determinations were always done.

The exercise was of two types: the leg flexion exercise in bed used by Bernhardt and pedaling on a bicycle ergometer (Sevringhaus type), with or without resistance. After the basal heat production had been determined the subject was instructed to flex one leg, bringing it forcibly back to the buttocks eight times in a minute, timed with a stop watch. At the end of each minute the alternate leg was then

exercised. This was repeated for twenty minutes, at the end of which time the mask was tightly adjusted and expired air was collected for a period of from five to eight minutes, while the patient continued with the exercise. This gave the height of the metabolism during the exercise. The patient continued the exercise until the necessary readings were recorded and checked, samples of the expired air were collected in sampling tubes and the gasometer was prepared for another test. A second test was then run for eight minutes, and at the moment of starting it the patient was

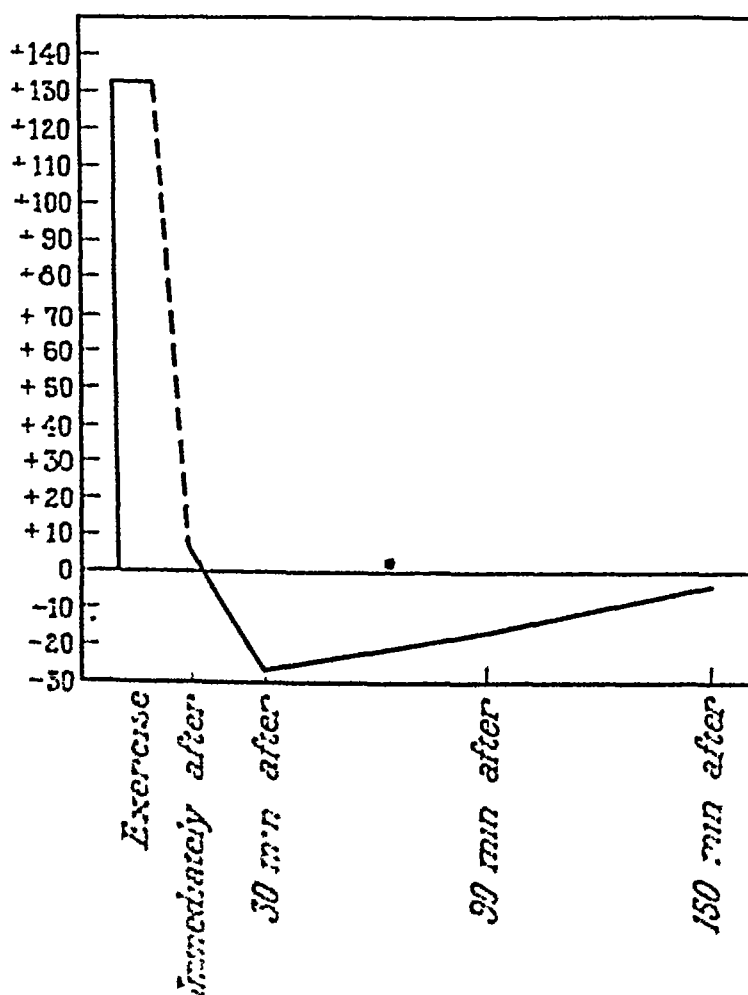


Fig. 1. (Case 23, Bernhardt). Negative phase of metabolism after exercise. The curve shows the depression of the metabolic rate from the day's "basal calories" during

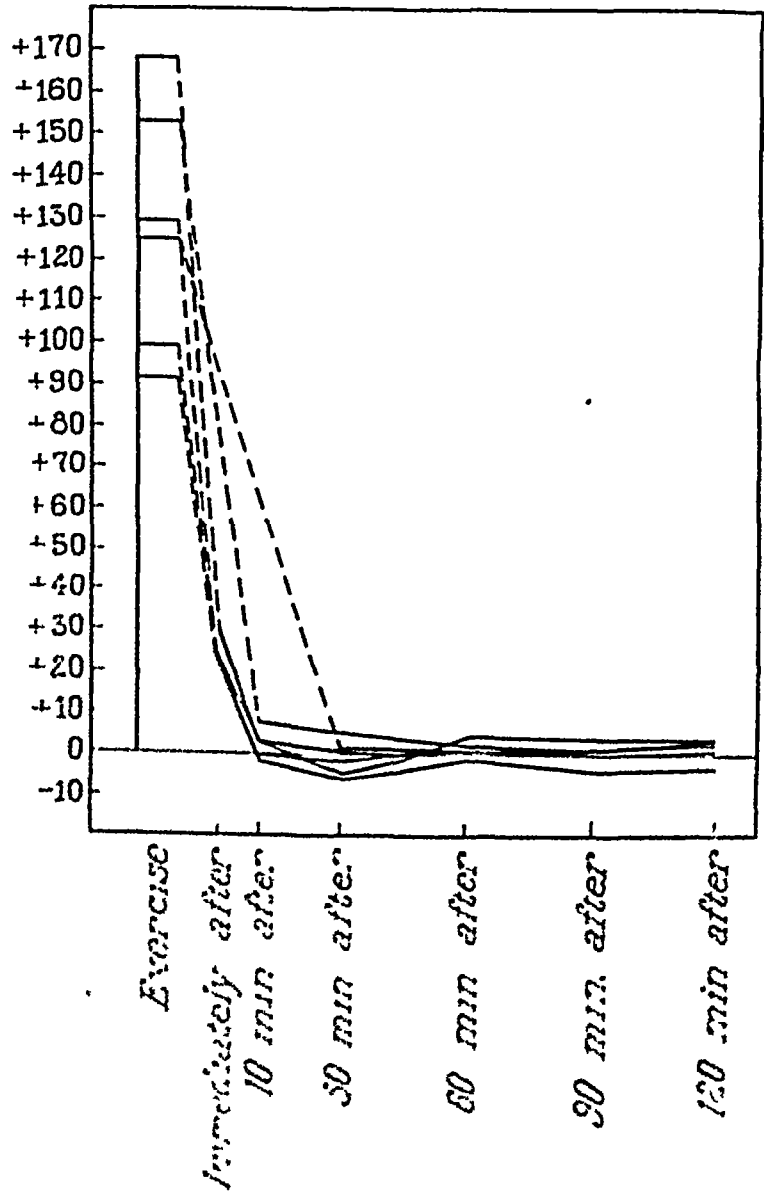
TABLE I
Effect of Exercise on the Rate of Heat Production

TOTAL CALORIES AND PERCENTAGE DEVIATION FROM THE AVERAGE OF THE DAY'S DETERMINATIONS OF THE BASAL CALORIES																						
CASE	DATE, 1931	AGE, YEARS, AND SEX	HEIGHT, CM	WEIGHT, KG	AVERAGE BASAL CAL- ORIES EACH HOUR	DETERMINATIONS AVER	BASAL CALORIES EACH HOUR ON DAY OF EXPERIMENT		DURING IMMEDIATELY EXERCISE AFTER													
							1	2	CALORIES	BASAL, %	CALORIES	BASAL, %	CALORIES	BASAL, %	CALORIES	BASAL, %	CALORIES	BASAL, %	CALORIES	BASAL, %	CALORIES	BASAL, %
LIGHT EXERCISE																						
1	5 6	60F	156.5	138.3	78.6	10	76.8	73.5	224.5	+199	74.4	-1	71.7	-5	74.0	-2	80.9	+8				
	5 11			137.4			80.1	79.1	127.2	+60	74.5	-6	79.3	-2	77.8	-2	77.2	-3				
	5 20			137.2			76.8	75.9	151.9	+99	77.7	+2	81.3	+6	79.4	+4	82.7	+8				
	5 28			136.4			81.5	80.9	131.3	+62	77.7	-4	79.6	-2	80.2	-1	82.9	+2				
	6 2			136.6			79.6	81.4	141.3	+76	83.6	+4	82.0	+2	88.4	+10	87.6	+9				
2	1 27	21F	173.0	133.9	84.0	20	89.4		230.8	+158	93.6	+5	92.9	+4	89.7	-1	91.1	+2				
	3 26			133.7			85.3		211.0	+147	92.5	+8	90.9	+6	87.5	+3	86.5	+1				
	3 30			132.4			94.7		288.6	+205	94.8		90.2	-5	86.8	-8	86.1	-2				
3	5 13	26M	183.0	113.9	76.9	12	76.5	77.3	238.5	+210	79.5	+3	78.5	+2	79.4	+3	80.8	+5				
	5 15			113.7			78.8	78.2	223.7	+185	77.5	-1	81.3	+4	77.8	-1	77.3	-2				
	5 19			112.8			76.7	76.2	237.8	+211	72.4	-5	74.6	-2	75.7	-1	75.2	-2				
	5 26			112.8			75.6	75.2	125.8	+67	83.6	+11	77.6	+3	75.7	-1	76.8	+2				
	6 3			111.1			76.1	76.9	215.3	+181	110.6	+45	78.3	+2	79.2	+1	76.5	+2				
	6 5			111.3			77.5	77.5	196.4	+153	104.6	+35	82.5	+6	77.7	-4	76.6	-1				
4	7 14	19F	161.0	78.2	58.5	14	61.4	58.9	155.6	+158	75.7	+26	60.1	-5	57.2	-1	58.6	-3				
	7 15			76.6			57.7	58.5	138.3	+138	73.1	+26	61.5	+6	57.3	-1	63.9	+10				
	7 16			76.3			58.6	57.2	111.2	+92	69.2	+20	58.8	+2	59.6	+3	59.2	+2				
5	7 3	31M	167.5	116.1	89.3	16	86.9	85.9	166.0	+92	106.7	+23	88.5	+2	90.2	+4	86.1	-1				
	7 9			116.7			91.9	90.0	187.0	+105	113.5	+25	88.5	-3	91.1	-1	89.8	-3				
	7 10			116.7			96.2	94.4	171.0	+79	117.0	+23	89.8	-6	82.9	-13	85.5	-10				
6	8 1	31M	165.5	55.6	50.5	2	50.1	50.9	113.9	+125	51.5	+2	51.2	+1	51.8	+3	51.2	+1				
HEAVIER EXERCISE																						
1	1 20	60M	156.5	112.4	77.7	6	78.3		330.0	+322	85.5	+9	82.5	+5	79.7	+2	84.5	+8				
	1 27			112.1			79.1		311.4	+123	86.6	+9	75.6	-1	81.4	+3	83.6	+6				
	1 28			112.1			81.0		295.0	+264	83.9	+4	81.5	+1	82.1	+1	83.1	+1				
	1 31			141.1			77.1		346.0	+319	90.7	+18	82.5	+7	78.5	+3	88.9	+15				
	1 32			140.1			71.8		331.1	+349	81.1	+13	80.7	+9	80.3	+9	87.6	+19				
	1 37			140.1			70.2	74.9	375.5	+117	88.8	+22	59.7	-18	90.1	+25	87.6	+19				
	1 41			139.7			71.2	75.1	103.1	+440	87.9	+18	81.9	+8	82.0	+19	77.3	+3				
	1 43			139.7			72.0	75.0	121.1	+117	81.9	+15	77.9	+6	71.8	-2	81.8	+15				
	1 47			114.7			71.7	76.0	263.9	+252	76.6	+2	71.8	+6	71.8	-2	78.8	+5				
2	1 33	30F	151.0	116.0	91.0	20	90.1		359.5	+298	103.2	+11	95.1	+5	92.3	+2	92.5	+1				
	1 34			111.9			90.5		321.6	+258	97.8	+8	92.1	+2	89.7	-1	89.0	-2				
3	4 8	21M	151.0	77.1	55.1	10	59.8	56.3	221.3	+241	60.1	+3	61.1	+5	57.5	-1	47.3	-19				
	4 9			77.1			51.1	54.1	198.1	+252	56.1		52.9	-6	51.5	-1	47.7	-15				
																	51.5	-1				

requested to stop the exercise This gave a measure of the heat production immediately following exercise Determinations followed 30, 45, 60, 90 and 120 minutes after exercise

When the bicycle ergometer was used the basal heat production was determined in bed and then the subject rode the bicycle with the mask in place The rate of pedaling with or without resistance was 58 to 60 revo-

lutions a minute timed with a metronome and stop watch At the end of twenty minutes' exercise the expired air was collected in the gasometer for a period of five to eight minutes, depending on the volume expired The mask was then removed and the patient returned to bed A determination of the heat production was made ten minutes after the exercise and thereafter as in the experiments with



the other type of exercise. In no case was the patient exhausted from the exercise. With the exception of cases 6 and 7 at least three experiments were done on different days.

Following light exercise there was a slight decrease in the heat production below the day's basal calories in only two instances in the experiments in case 2, March 30, and in case 5, July 10. However, the highest basal heat production was obtained in both of these patients on these days, for the former the increase over the average figure for calories each hour was 10.7 calories (13 per cent) and for the latter 6 calories (7 per cent) and, since a negative phase does not appear if the heat production after work is compared with the average basal metabolic rate of these two patients, we are led to conclude that the patients we studied did not manifest evidence of a negative phase in the heat production following light exercise.

With heavier exercise there was no evidence of a negative phase in cases 1 and 2. The single low value obtained in case 1 in the experiment on April 17, which was not confirmed by any of the other experiments done in this case, forces us to question the accuracy of the determination rather than accept it as a negative phase of only fifteen minutes or so duration. However, in case 7 there was decreased heat production occurring two hours after exercise in the experiment of April 28. Decreased heat production also occurred at the same time in the series of tests on the following day. At this time we were suspicious that the mask was not air-tight and

consequently immediately repeated the test (two hours and fifteen minutes after exercise) and the heat production was then only 3 per cent below the day's best basal heat production. The patient was a young girl who did not cooperate well.

The respiratory quotients in these experiments (table II) were elevated during or immediately after exercise in all experiments except one (case 1, experiment of April 17). This is probably explained by the quickened ventilation and consequent removal of carbon dioxide from the blood.¹⁰ The return of the respiratory quotient to the basal level was usually complete within thirty minutes after the exercise.

It has been pointed out by Benedict and Carpenter as well as by DuBois that any experiment involving repeated short period determinations of gaseous exchange after a change in basal conditions is subject to error from a variety of sources, but particularly because the actual basal condition, to which all other measurements must be referred, is extremely difficult to determine with the requisite precision. Strang and McClugage, in their very careful investigations on the specific dynamic action of food in abnormal states of nutrition also emphasize the importance of an accurate base line and state that negative phases exist only in so far as the basal values are elevated.

Bernhardt does not publish any data to show that his basal calories represent more than one determination and apparently only one of his patients was the subject of more than one experiment. In a later investigation con-

TABLE II
Effect of Exercise on the Respiratory Quotient

CASE	DATE 1931	BASAL RESPIRATORY QUOTIENT		DURING EXERCISE	IMMEDIATELY AFTER	10 MINUTES AFTER	30 MINUTES AFTER	45 MINUTES AFTER	60 MINUTES AFTER	90 MINUTES AFTER	120 MINUTES AFTER
		1	2								
1	5- 6	0.65	0.69	0.74			0.71		0.71	0.72	0.77
	5-14	0.71	0.73	0.76		0.79	0.71	0.76	0.76	0.75	0.75
	5-20	0.69	0.72	0.72	0.82	0.77	0.71	0.75	0.71	0.74	0.76
	5-28	0.71	0.69	0.72	0.85	0.79	0.70	0.69	0.71	0.70	0.76
	6- 2	0.64	0.70	0.73	0.83	0.81	0.74	0.71	0.73	0.77	0.75
2	3-25	0.74		0.82		0.75	0.73		0.72	0.74	0.72
	3-26	0.75		0.81		0.74	0.72		0.73	0.74	0.75
	3-30	0.73		0.82		0.74	0.71	0.73	0.71	0.74	0.75
3	5-13	0.71	0.71	0.82			0.72	0.71	0.73	0.76	0.78
	5-15	0.72	0.73	0.79			0.74	0.74	0.75	0.75	0.76
	5-19	0.72	0.74	0.81			0.75	0.75	0.75	0.74	0.75
	5-26	0.73	0.73	0.76	0.77	0.76	0.75	0.74	0.74	0.75	0.77
	6- 3	0.70	0.72	0.82	0.82	0.75	0.70	0.73	0.71	0.73	0.72
	6- 5	0.71	0.75	0.80	0.79	0.77	0.70	0.70	0.72	0.74	0.75
4	7-14	0.75	0.74	0.78	0.79	0.79	0.76	0.73	0.74	0.74	0.73
	7-15	0.74	0.73	0.76	0.78	0.78	0.78	0.73	0.73	0.77	0.74
	7-16	0.74	0.74	0.78	0.77	0.79	0.77	0.77	0.78	0.80	0.79
5	7- 3	0.73	0.73	0.79	0.83	0.83	0.72	0.71	0.74	0.73	0.75
	7- 9	0.75	0.76	0.83	0.90	0.80	0.73	0.79	0.75	0.77	0.77
	7-10	0.78	0.78	0.82	0.91	0.86	0.76	0.74	0.78	0.74	0.73
6	5- 1	0.78	0.78	0.82			0.79		0.76	0.77	0.75

HEAVIER EXERCISE

1	3-20	0.73		0.77		0.73	0.72		0.69	0.72	0.74
	3-27	0.66		0.79		0.74	0.66		0.67	0.69	0.70
	3-28	0.67		0.79		0.70	0.68	0.67	0.73	0.70	0.75
	4- 1	0.71		0.84		0.84	0.73	0.85	0.86	0.94	0.84
	4- 2	0.69		0.81		0.79	0.71	0.73	0.76	0.79	0.82
	4-17	0.79	0.76	0.76		0.81	0.71	0.76	0.77	0.76	0.78
	4-21	0.73	0.74	0.81		0.79	0.68	0.73	0.71	0.78	0.70
	4-23	0.70	0.77	0.77		0.79	0.69		0.74	0.72	0.81
	4-30	0.69	0.74	0.76			0.71		0.70	0.71	0.74
2	3-23	0.74		0.88		0.75	0.70		0.74	0.73	0.74
	3-31	0.74		0.82		0.74	0.70	0.69	0.70	0.72	0.72
7	4-28	0.71	0.76	0.87			0.70		0.71	0.73	0.72
	4-29	0.72	0.78	0.79					0.73	0.77	0.73
											0.73

ducted in Bernhard's Laboratory at The Mayo Clinic, Bernhardt himself was the subject and he again in one experiment observed a negative phase at a time when he was regaining weight lost in previous periods.

BASAL CALORIC DIETS

Several of Bernhardt's subjects, those with a diagnosis of endogenous obesity, held their weights or even gained, as was stated, when subjected to diets with caloric value equal to

their twenty-four-hour basal metabolism (Grundumsatz) They were not confined to bed and their failure to lose was attributed to compensation or economy by negative phases of the resting metabolism

We were able to hold three of our patients (cases 1, 2 and 3) in hospital for a period of 162 days The basal metabolic rates were determined repeatedly and the diet of each subject was made to equal his or her average basal heat production as determined, with particular attention paid to satiety values and adequacy of vitamins, minerals and protein Each subject occupied an isolated room in the metabolism division and, for the most part, the physical activity was supervised in the laboratory Two of these subjects were temporarily engaged as assistants in the laboratory The food was rigidly controlled and periodic examinations were made of the nitrogen and creatinine content of twenty-four-hour collections of urine and feces The salt given was 8 gm, and the fluids were made to equal 1,500 cc

The protocols of these observations, and the case records are given herewith (cases 1, 2, and 3) The weight loss, as shown graphically (figure 3), was that which could have been predicted from the knowledge of the basal metabolism and estimates of the extra energy resulting from the degree of physical activity A later recalculation of the total metabolism of these subjects gives figures which represent 141, 140 and 148 per cent, respectively, of their basal energy exchanges computed from the DuBois standards for their respective sexes, heights and weights (table III)

It is evident, however, that short periods of observation would have given entirely erroneous impressions of the total metabolism in these cases In case 2 the weight remained almost constant for 28 days, from December 1 to December 28, at 148 kgm, then dropped to 144.9 kgm by December 31 and held at this level until January 24 In cases 1 and 3 somewhat shorter, but nevertheless long, periods of constant weight occurred

WEIGHT LOSS DURING REST IN BED

In case 2, during an eleven-day period when the subject was required to remain in bed, the weight loss each day averaged 464 gm as contrasted to a daily loss of 122 gm, the average for the entire period of observation The patient in case 3 lost 900 gm a day for four days when he was in bed, as compared to his average loss of 143 gm a day In case 1 the average daily loss, during seven days in bed, was 614 gm, whereas the average loss each day for the entire observation was 103 gm This at first sight seems paradoxical With less energy expended by confinement to bed the rate of fat loss must decrease and weight loss should be retarded However, rest in bed serves to release water and thus temporarily at least the diminished rate of fat loss is obscured The phenomenon is the exact counterpart of what occurs with patients whose hearts are decompensated and one wonders how near to cardiac decompensation some of these very obese persons may be Direct measurements in case 2 revealed a striking diminution in the size of the legs during rest although putting edema was

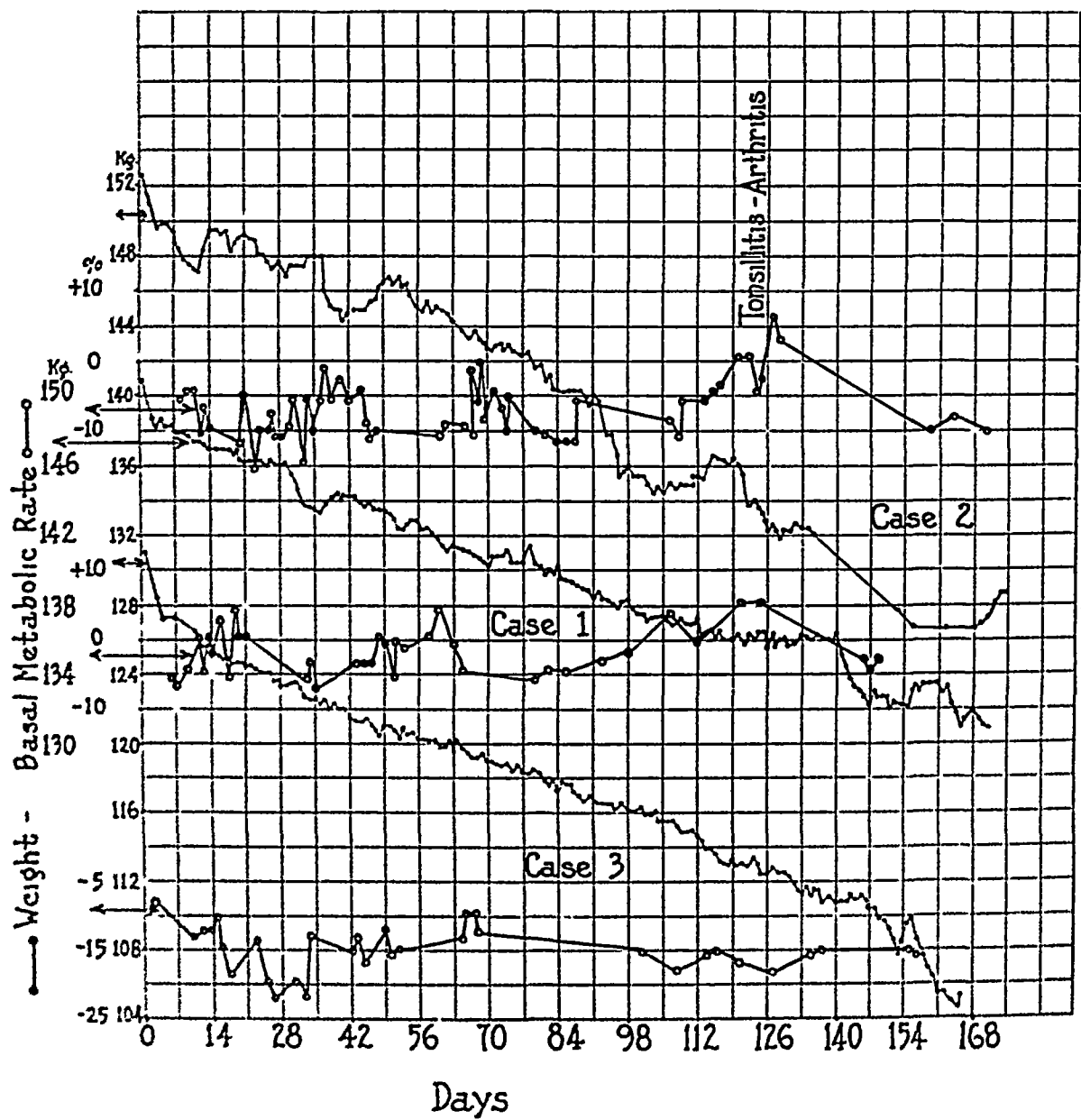


FIG. 3 Weight loss and basal metabolic rate in obesity

not observed. It is not improbable that this circulatory factor is often overlooked by physicians who are attempting to reduce obesity by diet and exercise, and that many instances of supposed resistance to reduction are accounted for by mild circulatory failure and imperceptible edema.

WEIGHT LOSS DURING ADMINISTRATION OF INSULIN

A possible effect of insulin on fat metabolism is suggested by the results

of gain in weight that follows its use in cases of cachexia. The benefit in cachexia may be explained by the resulting hypoglycemia and the effect of this on appetite and thus on total food consumption, but some evidence, especially the very high respiratory quotients (exceeding unity) that are obtained when insulin is given with a rich carbohydrate meal, is suggestive of a more direct action on fat metabolism. We gave insulin before meals to the subjects in divided doses of

TABLE III
Total Metabolism of Reducing Obese Subjects Calculated from Weight Loss and Food Consumption

CASE	AGE, YEARS, AND SEX	HEIGHT, CM	WEIGHT, KGV	DAYS REDUCING	WEIGHT LOSS, KGV *	AVERAGE WEIGHT LOSS EACH DAY, CM	FAT LOSS EACH DAY†	CALORIE EQUIVALENT OF DAILY FAT LOSS‡, CM	AVERAGE FOOD CALORIES EACH DAY	TOTAL CALORIES, 24 HOURS	STANDARD BASAL METABOLISM CALORIES 24 HOURS§	TOTAL CALORIES AS PERCENTAGE OF STANDARD BASAL METABOLISM	COMMENT
1	60F	156.5	139.5	162	167	103	90	837	1800	2640	1870	141	Up, patient in hospital, daily walks
2	24F	173.0	138.5	162	198	122	106	986	2060	3050	2180	140	Assistant in laboratory
3	26M	183.0	116.9	162	232	143	124	1153	2190	3340	2250	148	Assistant in laboratory

* The average of all body weighings or the weight after half the reduction was completed

† Fifty-seven per cent of average daily weight loss

‡ Grams of fat multiplied by 9.3

§ Computed from the Aub-DuBois standards for the given sex, age, height and weight

55 and 60 units respectively. In one case (case 3), retardation of weight loss was not observable during either of two periods of insulin of 27 and 37 days. In the other (case 1) with two periods of insulin of 12 and 30 days respectively, retardation was noted, but without additional data on the water balance its interpretation is not possible.

An interesting by-product of these experiments was the observation of a definite loss of tolerance for carbohydrate when insulin was withheld after it had been given for a time. It was demonstrated by a response to glucose test meals typical of mild diabetes. Tolerance tests made before the courses of insulin resulted in perfectly normal blood sugar curves. The abnormality resulting from the insulin injections persisted not longer than two or three days. The protocols are contained in the records of cases 1 and 3. The most plausible explanation of this would appear to be that during prolonged administration of insulin the islet mechanism is put at rest so that on discontinuing the injections the island cells are slow to respond to the stimulus of incoming carbohydrates. The phenomenon is analogous to that observed with other glands of internal secretion, the thyroid, the parathyroids and the anterior pituitary-gonad complex. Administering an endocrine product depresses the activity of the gland whose function it supplants. It is also analogous to the old phenomenon of vagabond or hunger diabetes and the diabetic-like reactions to glucose tolerance tests that are observed in nondiabetic subjects maintained on low carbohydrate diets.

That no actual involution or atrophy of the pancreas is involved is indicated by the rapid return to normal function.

ESTIMATION OF FOOD REQUIREMENTS

Estimates of calorie requirements have been based as a rule on the food consumption of groups of individuals, such as soldiers, or have been arrived at by adding to the calories of the basal metabolism a quota for the specific dynamic action of food and one for each of the various activities in which the individual is engaged. In either case considerable error is probably introduced. The figures obtained are often 100 per cent in excess of the basal metabolism, or from 3,000 to 4,000 calories a day for individuals of average build.

Another method is available when the subject is obese and on a sub-maintenance diet. This is to add to the calories of the food those accounted for by loss of weight. If the period of observation is long enough, and it should be extended over several months to avoid errors due to water retention, and if rigid supervision is maintained, so that the food consumption is actually known, this provides data which appear to be entirely reliable. It has been shown by Strang, McClugage and Evans that, when sufficient protein is supplied to obese subjects on reduction diets, the nitrogen intake and output remain in balance and tissue protein is not wasted. Also the creatinine excreted remains the same before and after the reduction, an indication that the muscle mass and the parenchymatous organs are not affected. It also appears from the observations of Strang, McClug-

age, and Evans, and from our own that the basal metabolic rate (heat production for each square meter of surface) is not lowered by weight reduction in obese subjects as it is in subjects of normal or less than normal weight (figure 3). The fat depots of the obese apparently serve as effectively as does ingested food in maintaining the normal level of heat production. All this being true, the weight loss provides a fairly accurate measure of the number of calories supplied by the organism, and these added to those allowed as food make a nearly accurate measure of the total metabolism.

An illustrative calculation in case 1 is as follows. A woman, aged 60 years, leads a sedentary life and is 156.3 cm in height. Her diet contains 63 gm of protein and has a total calorie value of 1,800. In a period of 162 days she loses from 147.8 to 131.1 kgm. Her mean weight is therefore 139.5 kgm, the total weight lost 16.7 kgm and the average weight lost each day 103 gm. Since the nitrogen of intake and output is balanced, the loss of weight is attributed to fatty tissue and if the water content of fatty tissue may be assumed to be 13 per cent (the average of the figures for human beings obtained by Bozenraad) then the daily loss of fat may be placed at 90 gm, which would contribute 837 calories to the day's energy expenditure. Adding this figure to the calories of the food gives 2,640 calories for the total metabolism, a value which exceeds by only 44 per cent the determined basal metabolism for twenty-four hours.

In table 3, estimates of total metabolism are made for the three principal

cases of this study. In two of them this exceeds 3,000 calories, but the surface areas of these subjects is relatively large, due to obesity; consequently the basal metabolism for 24 hours is large. Total metabolism, however, in no instance exceeds basal metabolism by more than 50 per cent. If we recalculate the data of table III, using standard body weights, the basal metabolism is found to range from 1,320 calories, for the inactive short woman aged 60 years, case 1, to 1,860 calories for the more active tall young man, case 3. If to these 50 per cent is added to cover total metabolism, the estimates are somewhat lower than those of the early students of metabolism and in better agreement with clinical experience. It has been our practice for many years to plan diets for patients with diabetes so that they will not exceed 50 per cent more calories than are needed for calculated basal requirements and with few exceptions this allowance has proved to be adequate for persons engaged in moderately active occupations, such as nurses and physicians.

REPORT OF CASES

Case 1. A woman, aged 60 years, was observed from October 7, 1930, to July 18, 1931. She was constitutionally obese, her height was 156.5 cm, and her weight 150.0 kgm, overweight 140 per cent. Her father was short and stout. A sister, 5 ft., 6½ inches in height, weighed more than 200 pounds, gained gradually, she had menstruated until the age of 65 years. Had been married twice, but had not been pregnant. Of five brothers one, short in stature weighed 250 pounds gained late in life. There were no familial diseases other than obesity. The patient's menstruation had always been irregular, at intervals of three to six weeks lasting one to two days (one period a month).

pain, and uninterrupted to date. At the age of 21 years she had weighed 135 pounds. Development of weight was normal until the age of 28 years. At the age of 36 years, she weighed 190 pounds, at 48 years, 325 pounds. This weight had been rather constant since then. She was engaged in active laundry work until the age of 48 years, afterward her life was sedentary. She complained of being unable to move quickly, of shortness of breath, palpitation on climbing stairs, often cough after exertion, and required two pillows at night. Edema of the ankles toward evening had been present in the last ten years. Her appetite was excellent. At the age of 55 years, on an attempt to reduce under a physician's care with diet and medicine, she lost 45 pounds in three months. On a second attempt to reduce at the age of 58 years, "eighteen day diet", no weight was lost.

The patient appeared to be intelligent. The blood pressure in millimeters of mercury was 150 to 120 systolic, and 110 to 70 diastolic. The Wassermann reaction of the blood and the Kahn test gave negative results. The concentration of hemoglobin was 100 per cent, leukocytes numbered 8,700 and erythrocytes 5,600,000 per cubic millimeter. Urinalysis gave negative results, the volume on unrestricted intake was approximately 1,500 c c. The hands and wrists were small, the

pituitary tumor. The average basal metabolic rate was -2 per cent.

Study of the metabolism extended over a period of 162 days (from February 6, to July 10, 1931). The patient was up and about the wards for daily walks. The diet consisted of 1,800 calories (determined basal expenditure), protein, 63 gm (1 gm for each kilogram of standard weight), sodium chloride 8 gm, and water 1,500 c c. The weight lost was 167 kgm. The average loss each day was 103 gm. The daily average of the nitrogen balance from March 2 to March 21, 1931, was $+0.87$ gm (nitrogen of feces not determined and nitrogen intake calculated as 10 gm daily). From April 9 to May 8, 1931, the daily average was $+1.08$ gm (nitrogen of feces and food determined). Daily creatinine determinations varied from 1.08 to 1.34 gm.

A maximum of 60 units of insulin was administered daily for 30 days (May 11 to June 10, 1931) with loss of weight of 0.8 kgm, the average loss each day was 27 gm. In another period a maximum of 55 units of insulin daily was administered for 12 days (July 2 to July 14, 1931). The total loss of weight was 0.8 kgm, the average loss each day 67 gm. The glucose tolerance* before and after the administration of insulin (63 gm of glucose given in the morning) was as follows:

DATE OF TEST	BLOOD SUGAR FASTING GM, 100 c c	BLOOD SUGAR ½ HOUR GM, 100 c c	BLOOD SUGAR 1 HOUR GM, 100 c c	BLOOD SUGAR 1½ HOURS GM, 100 c c	BLOOD SUGAR 2 HOURS GM, 100 c c	BLOOD SUGAR 3 HOURS GM, 100 c c
6-29-31	0.089	0.111	0.146	0.125	0.111	0.101
6-30-31	0.079	0.117	0.141	0.135	0.132	0.099
7-13-31*	0.115	0.149	0.194	0.211	0.250	0.231
7-14-31	0.099	0.155	0.178	0.196	0.196	0.168
7-15-31	0.101	0.130	0.137	0.158	0.125	0.111
7-16-31	0.083	0.125	0.151	0.157	0.151	0.125

*Insulin given from July 2 to July 14, 1931, maximal daily dosage 55 units. No insulin was given before glucose test meal July 13, 1931.

forearm was slightly increased in size, and the upper arm greatly increased. The feet were small, the legs were greatly enlarged with edema, varicosities and fat. The thighs were even more enlarged than the legs. Varicose veins were very prominent. Roentgenograms of the heart showed that it was 38 per cent oversize. There was no evidence of a

The weight lost during rest in bed from June 17 to June 24, 1932 (seven days), was from 130.5 kgm to 132.2 kgm (4.3 kgm). The average loss of weight each day was 614 gm. From July 8 to July 13, 1931 (five days in bed), the weight lost was from 133.6

*Blood sugars by new Folin method

to 131 kgm (26 kgm) The average loss of weight each day was 520 gm Table I shows percentage deviation of metabolic rate during and after exercise

Case 2 A woman, aged 24 years, was observed in hospital from November 23, 1930, to May 16, 1931 It was suspected that the obesity followed encephalitis Her height was 173 cm, and her weight 152.5 kgm, overweight 135 per cent Her mother had died of carcinoma at the age of 30 years There was no marked obesity in the family The patient had menstruated regularly for five years, since the age of fourteen, the interval between menstruations was 28 days, and the duration was five days This period decreased after influenza until a single pad sufficed During the last two years menstruation had increased and now lasted for one or two days, periodicity unchanged The normal weight of the patient was 135 pounds, but at the age of 19 years she had gained 100 pounds in one year There was no previous history of overweight At the age of 19 years the patient had influenza, with high fever, drowsiness, loss of hair, and laryngitis and was in bed for two weeks Diplopia had not been observed Subsequent recovery was slow (two to three months), and she tired easily, was very drowsy, the muscles became rapidly fatigued, and the eyelids drooped The hair grew rapidly again, and although the appetite had failed during the illness it was followed by an excessive desire for food, and gain in weight was rapid The patient suffered from headache She was emotionally normal Two months before coming to the clinic she was unable to raise her eyelids for two days Vision was unchanged

The patient appeared to be intelligent Her activity was diminished by excess weight The blood pressure was 130 systolic and 90 diastolic The Wassermann reaction of the blood and the Kahn test gave negative results The concentration of hemoglobin was 90 per cent, the leukocytes numbered 9,800 and erythrocytes 4,800,000 Urinalysis gave negative results, the volume on unrestricted intake after twenty-four hours was 750 cc The glucose tolerance test (65 gm of glucose) revealed the following: fasting blood sugar, 0.113, after half an hour, 0.156 after

two hours, 0.122 and after three hours, 0.080 gm Tests of the urine were negative for sugar Roentgenograms revealed that the thorax was normal, the size of the heart, approximately normal, and an unusual shape of the bones of the skull (ape-like) with considerable enlargement of the sella turcica The average basal metabolic rate was -8 per cent

Study of the metabolism, while the patient was employed as a laboratory helper, extended for a period first of 51 days (from December 5, 1930, to January 25, 1931) The diet consisted of 2,200 calories (110 per cent of the basal energy expenditure as determined later), protein, 65 gm (1 gm for each kilogram of standard weight) sodium chloride, 8 gm, and water, 1,500 cc The weight lost was from 148.4 to 144.7 kgm (3.7 kgm) The average weight lost each day was 73 gm In a second period from January 25 to May 16, 1931 (111 days), the diet consisted of 2,000 calories (determined on the basal expenditure), the amounts of protein, sodium chloride and water were the same The weight lost was from 144.4 to 128.6 kgm (15.8 kgm), the average weight lost each day was 142 gm The daily average of the nitrogen balance from March 9 to March 18, 1931, was +1.75 gm (feces not included, food nitrogen calculated as 10.4 gm daily) Creatinine determinations varied daily from 1.38 to 1.26

The daily average nitrogen balance from March 31 to April 2, 1931, was +0.34 gm (feces included food nitrogen calculated as 10.4 gm daily) Daily determinations of creatinine varied from 1.19 to 1.12 gm

The weight lost during rest in bed from December 27, 1930, to January 5, 1931 (nine days), was from 148.1 to 144.9 kgm (3.2 kgm), average loss each day 356 gm From February 22 to March 5, 1931 (11 days in bed) the weight lost was from 139.6 to 134.5 kgm (5.1 kgm) average loss each day 464 gm April 6 to April 28, 1931 (22 days in bed), the weight lost was from 132.1 to 124.7 kgm (7.4 kgm), the average loss each day 245 gm

Case 3 A man, aged 26 years, was observed from January 20 to September 22, 1931 It was suspected that his obesity was

of cerebral origin. His height was 183 cm and weight 131 kgm on admission, overweight 72 per cent. His mother was 5 ft, 7 inches in height, weighed 180 pounds and had a goiter. His father was 5 ft, 7 inches in height, and weighed 180 pounds. The patient had a sister who was of normal weight. At birth the patient had been injured with forceps. He had been overweight since childhood. For the last ten years he fell asleep when at work, slept for one or two minutes then was wide awake, he fell asleep when standing. This had occurred two or three times daily at any time, he lost consciousness abruptly and only realized that he had been asleep when he awakened. He sleeps the normal amount at night. His appetite is good. "does not eat more than the average man". In 1929 and 1930 he had tried several forms of treatment including diet and drugs, tablets by mouth, and hypodermic injections of a pituitary preparation three times weekly.

The patient seemed to be intelligent. He was afraid of losing his work as laborer as he could not keep awake. The blood pressure was 126 systolic and 80 diastolic, leukocytes numbered 10,000, and erythrocytes, 4,480,000. The Wassermann reaction of the blood gave negative results. The concentration of hemoglobin was 90 per cent. Urinalysis was negative, the volume with unrestricted intake was 1,150 c.c. Roentgenograms revealed calcification of the pineal body and normal sella turcica. The average basal metabolic rate was -15 per cent.

When undergoing study of the metabolism the patient was engaged as a laboratory worker. In the first period of 109 days (from January 22 to May 11, 1931), the diet consisted of 2,340 calories (123 per cent of the

basal energy expenditure as determined later), protein, 73 gm (1 gm for each kilogram of standard weight), sodium chloride, 8 gm, and water, 1,500 c.c. The weight lost was from 128.5 to 115 kgm (13.5 kgm), the average loss each day was 124 gm. In a second period of 53 days (from May 11 to July 3, 1931), the diet consisted of 1,900 calories (determined according to basal expenditures), protein, sodium chloride and water in similar amounts. The weight lost was from 114.7 to 105.3 kgm (9.4 kgm), the average daily loss was 177 gm. In a third period of 71 days (from July 12 to September 21, 1931) the calories, protein, sodium chloride and water were the same as those given in the second period. The loss in weight was from 106 to 93.6 kgm (12.4 kgm), the average loss each day was 175 gm. The daily average nitrogen balance from March 19 to April 20, 1931, was +0.5 gm (nitrogen of feces not determined and nitrogen intake calculated as 11.6 gm daily). From April 23 to May 4, 1931, the daily average nitrogen balance was -0.85 gm (nitrogen of feces and food determined). Creatinine determinations varied daily from 1.80 to 2.50 gm.

A maximal of 55 units of insulin was administered daily for 37 days (from March 8 to April 14, 1931) with total loss of weight of 2.9 kgm, the average loss each day being 78 gm. A maximal of 55 units of insulin was administered daily for 27 days (from May 30 to June 26, 1931), with total loss of weight of 4.5 kgm, the average loss each day being 167 gm. Glucose tolerance* before and after the administration of insulin (76 gm of glucose given in the morning) was as follows:

*Blood sugars by new Folin method

DATE OF TEST	BLOOD SUGAR FASTING GM, 100 c.c.	BLOOD SUGAR ½ HOUR GM, 100 c.c.	BLOOD SUGAR 1 HOUR GM, 100 c.c.	BLOOD SUGAR 1½ HOURS GM, 100 c.c.	BLOOD SUGAR 2 HOURS GM, 100 c.c.	BLOOD SUGAR 3 HOURS GM, 100 c.c.
5-28-31	0.066	0.126	0.140	0.103	0.085	0.054
5-29-31	0.077	0.141	0.144	0.109	0.081	0.047
6-25-31*	0.068	0.138	0.181	0.196	0.203	0.114
6-26-31	0.074	0.150	0.175	0.209	0.194	0.099
6-29-31	0.072	0.119	0.140	0.112	0.109	0.067

*Insulin given from May 30 to June 26, 1931, maximal daily dosage 55 units. No insulin was given before the glucose test meal, June 25, 1931.

From June 21 to June 23, 1931, was a period of extreme heat. Activity continued and the patient gained weight from 107.8 to 109.9 kgm. When in bed from June 24 to June 28, 1931 (four days), he lost weight from 109.9 to 106.3 kgm (3.6 kgm), the average loss each day was 900 gm.

Case 4 A girl, aged 19 years, was observed in hospital from July 5 to August 8, 1931. She was constitutionally obese, her height was 163 cm, and her weight 78.3 kgm, overweight 40 per cent. One sister was obese until she married when she became normal. Her mother formerly was obese, and two maternal cousins were overweight. There were no familial metabolic diseases other than obesity. Menstruation had occurred at the age of 15 years, and the flow was scanty and at intervals of two to three months. She had been overweight since infancy, reduction had been attempted at the age of 12 years and again at 16 years. She stated that she did not eat more than her associates. She had had mastoiditis at the age of seven years, measles at 14 years, epileptic attacks at 14 years, one attack when 15 years, then more frequently until treatment was instituted with phenobarbital, grains 3, daily. Headache or polyuria had not been present. She had received treatment with thyroid extract at the age of 17 years, at which age she also had pneumonia. She had never had encephalitis or injuries to her head.

The patient appeared to be intelligent. The fat was distributed symmetrically. The blood pressure was 106 systolic and 70 diastolic, erythrocytes numbered 4,600,000 and leukocytes, 9,000. The Wassermann reaction of the blood and the Kahn test were negative. The concentration of hemoglobin was 87 per cent. Urinalysis gave negative results. The glucose tolerance test (56 gm of glucose) revealed the following: fasting blood sugar, 0.054, after half an hour, 0.106, after one hour, 0.116, after two hours, 0.071, and after three hours, 0.070 gm. Tests of urine were negative for sugar. Roentgenograms revealed that the sella turcica was normal. The average basal metabolic rate was -16 per cent.

Studies of the metabolism extended from July 20 to August 12, 1931 (twenty-three

days). The diet consisted of 1,350 calories, protein, 74 gm (1.3 gm for each kilogram of standard weight), sodium chloride, 8 gm, and water, 1,500 cc. The weight lost was from 75.7 to 74.2 kgm (1.5 kgm), the average loss each day was 65 gm.

Case 5 A woman, aged 31 years, was observed from June 8 to July 11, 1931. She was constitutionally obese and was gaining weight, her height was 167.5 cm, and her weight 121.2 kg, overweight 92 per cent. Her parents and seven brothers and sisters were all of normal weight, one sister weighed 200 pounds. There were no familial metabolic diseases other than obesity. Menstruation began at the age of 13 years, and flow was always scanty. She was "stout" as a child, weighed 180 pounds at the age of 19 years, and 240 pounds at the age of 25 years in her first pregnancy. She had had rheumatism at the age of 27 years, and a relapse with mental disturbance (chorea?) for one year afterward with loss of weight of 100 pounds. She regained her weight of 260 pounds when in her second pregnancy, and weighed 268 pounds at the age of 30 years. The patient had had "acute articular rheumatism" in 1927, which confined her to bed for three months. This was followed by mental disturbances for one year. There was no intolerance to heat, no polyuria, or nocturia. Her appetite is excessive, she likes sweets, fats and pastries. She has never tried to restrict the intake of food.

The patient appeared to be of mediocre intelligence. A cystic adenoma of the thyroid gland, 5 cm in diameter, and varicose veins of the legs were present. The distribution of fat was uniform. The blood pressure was 124 systolic and 80 diastolic. The Wassermann reaction of the blood and Kahn tests gave negative results. The concentration of hemoglobin was 80 per cent, leukocytes numbered 7,200 and the erythrocytes 4,740,000. The average basal metabolic rate was -13 per cent.

Study of the metabolism extended from June 8 to June 16, 1931, with the patient up and about. She was permitted to select her food for five days, and the average daily consumption was 1,730 calories. She lost weight from 119.8 to 115.4 kg (4.4 kg).

She was readmitted to hospital from June 28 to July 11, 1931. Diet contained 4,000 calories (determined on the basal expenditure +100 per cent), and protein, 60 gm. She gained in weight from 117 to 118.4 kgm.

Case 6 A woman, aged 32 years, with anorexia nervosa, was observed from October 13, 1930, to June 18, 1931. Her height was 165.5 cm, and her weight 39.2 kgm, underweight 37 per cent. There were no familial metabolic or mental diseases. Menstruation began at the age of 13 years, and had been regular until two years ago, then irregular and scanty from October 1, 1930, to April 1, 1931, following which it had been regular. The patient had been married for nine years and had one healthy child. There had been no other pregnancies. The loss of weight occurred in the preceding three years. The weight had been 67 kgm. Her appetite was good, but she restricted the intake of food because of distress after eating, this led to a diagnosis elsewhere of mucous colitis. Constipation was marked, and had been treated unsuccessfully elsewhere by diet, irrigations of the colon and desiccated thyroid extract.

The patient appeared to be acutely ill and cachectic. The blood pressure was 100 systolic and 60 diastolic, leukocytes numbered 5,100 and erythrocytes 4,140,000. The concentration of hemoglobin was 82 per cent. Urinalysis gave negative results. The Wassermann reaction of the blood was negative. Roentgenograms of the thorax, gallbladder, stomach and colon were negative. Roentgenologic examination of the colon and ileocecal region gave no evidence of stasis. The basal metabolic rates in December, 1930, were -23 and -22 per cent. May 1, 1931, the basal metabolic rate was -14 per cent.

Study of the metabolism extended over a period of 89 days (from February 22 to May 22, 1931) with the patient ambulatory. The diet contained 400 gm fruits and vegetables, 66 gm protein, 225 gm fat, calories 3,290. The weight gained was from 39.2 to 57.6 kgm (18.4 kgm) an average daily gain of 207 gm. Two hundred seven grams of body fat represent 1,674 calories. The total intake of calories, 3,290, minus 1,674 gives 1,616 calories for total expenditure, 1,616

minus 1,110 (basal expenditure) equals 506 calories for work, or 46 per cent of the basal expenditure.

Case 7 A woman, aged 23 years, was observed from April 16 to May 4, 1931. She was constitutionally obese, her height was 154 cm and her weight 80 kgm, overweight 51 per cent. There was no familial history of obesity or other disease of metabolism. Menstruation had begun at the age of 13 years, and was regular until two years before observation, then the intervals lengthened, and the flow decreased to a scanty discharge for one day only. Her weight had been normal at the age of 20 years, and gain began when she was convalescing from a fractured leg, and progressed intermittently, the most rapid gain was made shortly before observation. The patient had occasional frontal headache, and was easily fatigued and nervous.

The patient appeared to be intelligent. The distribution of fat was uniform. The blood pressure was 102 systolic and 72 diastolic, leukocytes numbered 6,600, and erythrocytes, 4,560,000. The concentration of hemoglobin was 89 per cent. The Wassermann reaction of the blood and the Kahn test were negative. Roentgenograms of the sella turcica did not reveal any abnormalities. The average basal metabolic rate was -14 per cent.

SUMMARY AND CONCLUSIONS

1 The heat production following light and heavy exercise of obese subjects studied by us does not tend to drop below the basal level at any time during the two hours after exercise.

2 Three obese subjects, chosen for their "endogenous" characteristics were held under strict supervision in the metabolism division of the hospital for a period of 162 days. Their diets were arranged to provide a total of calories which would closely approximate their basal metabolism for 24 hours, with particular attention paid to satiety values and adequacy of vitamins, minerals and protein. Re-

duction in each instance proceeded at a rate which was anticipated from conventional calculation of the total metabolism involved

3 The rate of weight loss was seldom regular. Periods of several days frequently intervened when the weight remained stationary or even increased. One such period was 28 days. That these are to be accounted for by water retention is indicated by the influence of enforced rest in bed. An accelerated rate of loss invariably accompanied periods of rest in bed and corresponding retardation of weight loss was seen in periods of increased activity. The paradox is explained by relative circulatory insufficiency.

4 Insulin in doses of 20 units before each meal failed to alter significantly the rate of weight loss in one

case and was of doubtful influence in another.

5 The administering of insulin for periods of from 12 to 30 days was followed by temporary loss of tolerance for carbohydrate, so that responses to glucose tolerance tests were obtained typical of diabetes mellitus. The phenomenon is explained by diminished irritability of the rested pancreas, analogous to that observed after periods of carbohydrate starvation. Recovery of normal irritability is a matter of only two or three days.

6 Estimates of total metabolism, based on long periods of observation of weight loss of obese individuals on submaintenance diets, are in better agreement with clinical experience than the higher estimates of earlier students of metabolism.

BIBLIOGRAPHY

- ¹BENEDICT, F. G., and CARPENTER, T. M. Food ingestion and energy transformations, with special reference to the stimulating effect of nutrients, 1918, Carnegie Institution of Washington, Washington, D. C.
- ²BERNHARDT, HERMANN. I. Zum Problem der Fettleibigkeit (Zugleich ein Beitrag zur Frage des sogenannten "Grundumsatzes"), *Ergebn d inn Med u Kinderh*, 1929, **xxvi**, 1-55.
- ³BERNHARDT, HERMANN. New concepts concerning the pathogenesis of obesity and the problems of basal metabolism, *Endocrinology*, 1930, **xiv**, 209-225.
- ⁴BOOTHBY, W. M., and BERNHARDT, HERMANN. Stoffwechselanalysen am Gesunden unter verschiedenen Bedingungen, *Ztschr f klin Med*, 1931, **lxvi**, 219-240.
- ⁵BOOTHBY, W. M., and SANDIFORD, IRENE. Laboratory manual of the technic of basal metabolic rate determinations 1920. W. B. Saunders Co., Philadelphia.
- ⁶BOZENRAAD, O. Über den Wassergehalt des menschlichen Fettgewebes unter verschiedenen Bedingungen, *Deutsch Arch f klin Med*, 1911, **ciii**, 120-123.
- ⁷DUBOIS, E. F. Recent advances in the study of basal metabolism, *Jr Nutr*, 1930, **iii**, 217-228.
- ⁸JOHNSTON, MARCARET W., and NEWBRIGHT, L. H. The determination of the total heat eliminated by the human being, *Jr Clin Invest*, 1930, **viii**, 147-160.
- ⁹LAUTER, S. Genesis of obesity, *Deutsch Arch f klin Med*, 1926, **cl**, 315-365.
- ¹⁰LUSK, GRAHAM. The elements of the science of nutrition 1928, Ed 4. W. B. Saunders Co. Philadelphia.
- ¹¹MCCLEGG, H. B., BOOTH, GEORGE, and EVANS, F. A. Creatinine excretion in abnormal states of nutrition, *Am J Med Sci*, 1931, **ccxiii**, 349-355.
- ¹²NEWBRIGHT, L. H., and JOHNSTON, MARCARET W. The nature of obesity, *Jr Clin Invest*, 1930, **viii**, 197-213.

- ¹³NEWBURGH, L. H., JOHNSTON, MARGARET W., and FALCON-LESSES, MARK Measurement of total water exchange, *Jr Clin Invest*, 1930, viii, 161-196
- ¹⁴SEVRINGHAUS, E. L. Human energy metabolism I. A simple bicycle ergometer *Am Jr Physiol*, 1927, lxxx, 347-354
- ¹⁵STRANG, J. M., McCLUGAGE, H. B., and BROWNLEE, M. A. The specific dynamic action of food in abnormal states of nutrition, *Am Jr Med Sci*, 1931, clxxxii, 49-81
- ¹⁶STRANG, J. M., McCLUGAGE, H. B., and EVANS, F. A. Further studies in the dietary correction of obesity, *Am Jr Med Sci*, 1930, clxxix, 687-694
- ¹⁷STRANG, J. M., McCLUGAGE, H. B., and EVANS, F. A. The nitrogen balance during dietary correction of obesity *Am Jr Med Sci*, 1931, clxxxi, 336-349

The Depression and Public Health

“THE progress of public health is influenced by many factors, social, economic, and industrial as well as medical, sanitary, and biological. The adverse effects of unfavorable economic conditions on individual and community health have been demonstrated so frequently that a financial depression such as has been experienced by the United States would be expected to have deleterious results on national vitality.

“To date the anticipated has not occurred. The year 1931 was, in fact, apparently one of the most healthy in our history. Not only was there no undue prevalence of disease and no widespread occurrence of epidemics, but death rates were lower. The mortality from tuberculosis, a disease peculiarly involved in social and economic conditions, declined from 71 to 67 per 100,000 population, and infant mortality, one of the most sensitive indices of sanitary progress, continued to show a favorable trend.

“This auspicious health record during two years of depression should not, however, be permitted to lull us into a false sense of security. The results of malnutrition, improper housing, inadequate clothing, insufficient recreation, unhealthy mental and emotional reactions, and the curtailment of necessary health services are not reflected immediately in the state of the nation's health, but these conditions, which unquestionably exist today, cause a definite lowering of the vital resistance of the people and may make them a ready prey to disastrous epidemics, should they occur. An outbreak of influenza at the present time might prove devastating.

“Although the incidence of communicable and organic diseases has not yet appreciably increased, there seems to be a demonstrable increment in mental disorders. No general rise in mental cases of institutional severity has been reported, but mental hygienists believe and social surveys indicate real evidence of an increase in nervous disturbances and the milder mental diseases. Paroles in all mental hospitals have fallen off and there have been decided increases in the admissions to institutions for the feeble-minded. The depression is unquestionably engendering fears and anxieties that are undermining individual and family security and taxing the adaptive capacities of all classes of the population. These conditions tend to become accentuated as the depression continues. The suicide rate in 1931 was considerably higher than in the previous year.”

(From a statement compiled by JAMES A. TOLBY for the United Educational Program of the National Social Work Council. See *Jr of Social Hygiene*, 1932, viii, 118-119.)

Insulin in Malnutrition

Further Observations¹

By ROY D. METZ, M.D., *Detroit, Michigan*

WHEN Banting and Best² made their outstanding contribution to scientific medicine and changed the diabetic patient of today to a living and not a dying diabetic, they little dreamed that the usage of insulin would invade the entire realm of medicine. It was about one year afterwards that Pitfield³ made successful use of insulin in infantile inanition. He noted that diabetic patients on insulin treatment often gained weight at a phenomenal rate even when the food intake was not excessive. Then Marriott⁴ reported uniformly good results in infantile athrepsia with the usage of insulin. Almost coincidentally, Barbour⁵ reported the successful administration of insulin subcutaneously in undernourished non-diabetic children. In 1925, Falta⁶ reported the non-diabetic usage of insulin in adults with uniform success. Since then, numerous publications have been presented dealing with the non-diabetic usage of insulin in various forms of malnutrition, both primary and secondary. While some of the authors are very conservative in their predictions, most of them have been more or less enthusiastic in regard to the possibilities

of insulin in undernourished non-diabetic patients. Frank and Wagner⁷ have published recently a monographic review of the German literature in reference to insulin so used. They have discussed its theoretical aspects more thoroughly, it seems, than have any other authors.

While most publications have been based upon observations in the hospital where close observation was possible, there seems to be no particular reason why insulin could not be utilized safely and efficiently by physicians in general practice. Jacobsen,⁸ for instance, feels that the administration of small doses of insulin with extra food in order to prevent shock is adapted for use in private practice without deleterious effects. Ceccarelli,⁹ too, advises the administration of insulin in emaciation and cites an especially favorable result in a patient with marked emaciation following cholecystitis with calculus. Toscano¹⁰ has reported excellent results with the use of insulin. He found that patients with malnutrition and without other evident disorders reacted most favorably and that the sense of well-being which resulted was frequently of greater importance than the increase in weight.

Favorable results from the use of

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insulin in the treatment of the malnutrition of children were reported even before its usage was considered seriously in adults. Careddu and Giua¹¹ reported that insulin brought about a regular and constant increase in weight with the formation of good subcutaneous tissue and improvement not only of the general condition but also of the resistance of the child. They also reported an increased intestinal tolerance for carbohydrates. Amici¹² has reported the beneficial effect of insulin in infantile athrepsia. He secured a notable increase in weight in a short time, with rapid improvement of the general condition. He comments particularly on its stimulative influence upon the appetite and upon general activity. Roi¹³ summarized his observations by stating that insulin stimulated glycogenesis and glycogenolysis, and brought about greater utilization of carbohydrate with consequent increased appetite, increased tissue turgor and the formation of a fat reserve. He also concluded that it acted favorably on catabolism especially in a state of acidosis, corrected possible dysfunction of the pancreas favoring the absorption of fat by the intestinal villi and stimulated the whole endocrine system.

If these favorable reports are true, we must no longer limit the use of insulin to the treatment of diabetes alone. We may look upon it as a biologic product unrestricted in its action to one system or organ in the body. Its influence apparently extends over the entire organism to a degree which we do not sufficiently understand or appreciate. While it seems to have been beneficial in the case of

many patients with malnutrition treated in the hospital, its usage in ambulatory patients has been inaugurated with fear and hesitancy. This may be due to the fact that there is a certain amount of novelty and mysticism associated with its usage in non-diabetic patients.

It appears that the primary indication for the utilization of insulin is the presence of malnutrition from almost any cause. It must be remembered that best results may be expected in patients without outward evidence of organic disease. The first item to be considered is the degree of anorexia present. This is important, because patients with a good appetite appear to react most favorably to small doses of insulin. It seems to render more efficient the absorption and utilization of carbohydrates, perhaps through pancreatic stimulation and increased intestinal peristalsis. In those patients with greater anorexia, larger doses seem to produce better results in direct proportion to the degree of anorexia. This seems to be caused by gastric hyperperistalsis, with its consequent hunger contractions. In such a condition, Short¹⁴ advises, it is important to have a diet rich in fats, for oftentimes such hunger is quickly allayed with relatively small quantities of carbohydrate.

Other items to be considered are the amount and frequency of the doses. There are two acceptable methods of treatment. The first, probably the best adapted for ambulatory patients, is the injection of one dose daily before the noon meal. This should be given approximately 20 minutes before eating in order to allow sufficient time for

absorption with consequent lowering of the blood-sugar preparatory to the new supply of carbohydrates. This method is more convenient and probably minimizes the possibility of an accumulative action of insulin.

It is usual to begin with doses of 5 or 10 units of insulin and to increase to 15 or 20 units according to the tolerance. It is not advisable to cause a hypoglycemia, although this may be easily and quickly checked by the administration of carbohydrate. It is preferable to maintain a high dosage and encourage the patient to ingest more than the usual amount of food. In any case, the dosage should be kept within the individual tolerance. While the sympathetico-suprarenal apparatus seems to liberate sufficient glucose from the liver-glycogen to take care of the ordinary hypoglycemic condition, even if no carbohydrate is ingested, the reaction may have an unfortunate psychic effect upon the patient.

The second method of treatment is to give two or more smaller doses each day. Ten units of insulin may be given before each of any two meals or before each of the three meals. If it should be given 20 minutes before the meal, there will be little or no danger of hypoglycemia. Nevertheless, carbohydrate should always be at hand for its psychic effect if for no other reason. This method causes greater inconvenience to the patient and has not proved as satisfactory as the administration of one larger dose each day. Of course circumstances alter cases, and each patient must be treated individually.

In either of the above procedures,

the physician should personally initiate the treatment in order to ascertain the tolerance and optimal dosage for the individual patient. When this is accomplished, he may teach the patient how to administer the insulin to himself, particularly emphasizing the necessity for accuracy of dosage, the necessity for cleansing the field of injection, and the importance of varying the sites of injections in order to avoid causing local fibrosis and atrophy of the subcutaneous fat.

The patient may then go about his work as usual, reporting to the physician at regular intervals for a check-up and for any instructions or changes deemed advisable. Although the patient may continue his work, the rate of gain in weight seems to depend greatly upon the energy expended at his work. It seems that the clerical patient reacts more satisfactorily than the one doing hard manual labor. No deleterious effects have been noted even when the therapy was continued over a long period of time. The length of the course depends upon the individual reaction to its usage and the speed with which the exogenous insulin causes an increased endogenous production of insulin to bring about a satisfactory weight or a progressively increasing weight, however small this may be.

There are three possible complications which must be ever present in the mind of the physician who administers insulin. The possibility of inducing hypoglycemia is of primary importance. This is first manifested by a sense of weakness and extreme fatigue. It usually occurs about two hours after the injection. If the tol-

tient is walking, he feels that he cannot progress a step further¹⁵ Restlessness begins and the hands tremble Perspiration follows with an intense sensation of hunger There is impaired visual acuity, and some patients may even complain of diplopia There may be vertigo, ataxia, nausea, vomiting, and epigastric distress Mental confusion may be shown by incoherent speech, irritability, or some irrational action The sequelae are those of stupor and coma No patient should be permitted to progress to this stage There should always be available carbohydrate, such as cubed sucrose or candy, for immediate ingestion This is particularly important when the patient leaves his usual source of carbohydrate for a walk, an automobile ride, or for some other reason By the ingestion of such carbohydrate, any hypoglycemia can be quickly and efficiently counteracted

The second complication is allergy¹⁶ In patients with allergic manifestations, such as urticaria, hay-fever, or asthma, insulin should be given with greater caution Crystalline insulin¹⁷ has been prepared and its chemical properties studied It seems extremely probable that insulin is a well defined protein and that its physiologic activity is a property of the insulin molecule itself or of some special group within the complex molecule Grishaw¹⁸ has recently reported allergic manifestations to insulin He cited a definite reaction in a diabetic patient Through experimentation with insulin from different sources and by different producers, he concluded that the insulin itself was not the causative agent in the allergic manifestation but that the

latter was due to some precipitable substance contained therein

Although the foreign protein in insulin has been reduced to a minimum by our modern efficient producers, it still contains some, and a local or general reaction may follow its use The local manifestation is usually an erythematous area at the site of the injection This may progress to a wheal or even to a general urticarial eruption with edema of the face, intense itching, and gastro-intestinal distress It usually appears about ten minutes after the injection and is relieved satisfactorily by calcium lactate orally Epinephrine may be used, but it is rarely necessary In the future, it is hoped that the animal source of the insulin will be marked on its container Then, should the patient be sensitive to beef protein, pork protein may be well tolerated, and vice versa Should there be a hypersensitivity to all of the usual sources of insulin, desensitization must be accomplished by a series of intradermal injections of insulin Jeanneret¹⁹ reported a patient so desensitized with no reaction after the seventeenth injection

The third complication to be borne in mind is the condition of the myocardium, particularly in angina pectoris and aortic insufficiency Experiments have shown that insulin diminishes the quantity and viscosity of the blood, with a decrease in the blood pressure The heart may enlarge to the left with an acceleration in its rate Transitory diastolic murmurs may even appear A routine cardiac examination requires so little time that it should be done in all cases Myo-

cardial contraindications will be found very infrequently. If a hypoglycemia is prevented, there is little need of fear in reference to the myocardium.

While the beneficial effects of insulin in malnutrition seem to be conceded and proved, we must still resort to theory, conjecture, and speculation in order to explain how its effects are produced. Falta²⁰ believed that insulin checks the elimination of sugar in the liver and promotes its absorption by muscles and other tissues. Depisch and Hasenohrl²¹ advanced the counter-regulation theory against insulin. In this, the counterregulation promotes the elimination of glucose in the liver and checks its absorption in the tissues. They theorized that the assimilatory insulin system with its nervous regulation stands in the center of carbohydrate metabolism and therefore promotes the absorption of glucose in the liver and in the tissues. Against this, there is the action of the sympathetic nervous system and the secretion of the suprarenals, the posterior lobe of the hypophysis, and the thyroid gland in the liver, and the action of the secretions of the suprarenals and thyroid in the tissues. Their idea was not at all unlike the conception of Cannon²² in which he explained the antagonistic action of insulin and epinephrine.

Columba²³ has recently made an interesting observation. He obtained an insulin-like extract from obese and undernourished patients. Experimentally, he noted that this extract was less potent in the obese, and he felt that the decreased potency should be regarded as an expression of a latent state of functional insufficiency of the

pancreas, or diabetes mellitus. His observation thus strengthens the conception advanced by Fonseca²⁴ that there is a more or less direct relationship between obesity and diabetes.

Instead of looking upon malnutrition as a state of hypoinsulinism, it may be considered a state of hyper-suprarenalism. Such a condition would have a tendency to free the glycogen from the liver and muscles into the blood stream, where it could and would be readily oxidized. Under such circumstances, the exogenous insulin in insulin therapy would not only help to counteract the supply of epinephrine present but it would also stimulate the islands of Langerhans to greater activity so that a more normal and delicate balance would result between these antagonists with an approach to normal of the entire body economy. While an imbalance is probably present, it has not been determined whether it is due to the endocrine glands alone, to the autonomic nervous system alone, to a combination of both of these factors, or to some other cause. Hyman and Kessel²⁵ have taken a rather pessimistic attitude when they considered autonomic imbalance congenital and specific therapy not clinically available because we are ignorant of the chemical and hormonal factors which control the autonomic nervous system normally and stimulate it in emergency.

Although our knowledge of the relationship of the various endocrine glands to carbohydrate metabolism may be insufficient and attempts to evaluate disturbances in these mechanisms may be clinically somewhat difficult, there is at present adequate

reason to assume that all carbohydrate enters the blood stream as glucose. Here a variable portion is oxidized directly or indirectly into carbon dioxide and water, while the remaining portion is stored in the liver and musculature as glycogen.²⁶ Liver-glycogen may be reconverted into glucose and liberated into the blood stream as such through the action of epinephrine according to the demands of the organism. In the musculature, epinephrine causes the trembling or the contraction of muscles or groups of muscles, with the formation of lactic acid from muscle-glycogen. This acid²⁷ enters the blood stream and is reconverted into glycogen by the liver, from which it may be liberated as glucose. It would appear, therefore, that the tremors and convulsions of a hypoglycemia are protective mechanisms for the organism. The muscles may thus be looked upon as a reserve supply for glucose when too great a demand is being made upon the liver.

It may be concluded that insulin may be used advantageously in the non-diabetic patient. It extends its influence over the entire organism to a degree which we do not sufficiently understand or appreciate. It is probable that the gain in weight and the improved general well-being is due to more efficient absorption and utilization of carbohydrates, but we do not know how these are accomplished. While the optimal results are obtained in the hospital, the treatment appears adaptable for employment in private practice in ambulatory patients with average intelligence. In the ambulatory patient, the general effect of the treatment is similar to that upon the patient

treated in the hospital with reference to the increase in weight and the improved general well-being, but it is apparently less rapid and less satisfactory. A few case reports will illustrate the beneficial effect of insulin upon certain ambulatory patients.

CASE REPORTS

Case I A mechanic, aged 39 years, entered the Marine Hospital because of cough, weakness, and loss of weight. He appeared ill and was definitely undernourished and anemic. A diagnosis of pulmonary tuberculosis could not be confirmed. He was constantly having small superficial ulcers on the buccal mucous membrane. His condition was more or less stationary when insulin-treatment was inaugurated before the noon meal. The anemia began to improve, the ulcers healed, and the cough became less marked. He became stronger with an average gain in weight of over 3 pounds a week.

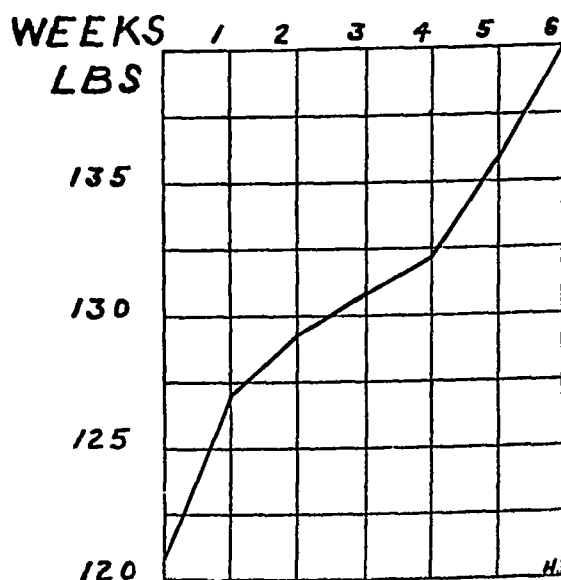


FIG 1 Weight curve in Case I

Case II A Canadian automobile mechanic, aged 37 years, entered the Marine Hospital because of abdominal discomfort and distress particularly after a bulky meal. He had had several surgical operations in the past eight years without marked relief. Physical examination revealed an unstable nervous system, malnutrition, and several postoperative ab-

dominal scars. He was much discouraged when insulin treatment was started. His general condition began to improve immediately. Even with unusually bulky meals, his abdomen became progressively more comfortable. He became stronger and his philosophy of life approached normal. He was at first given 20 units before the noon meal. Because of several mild reactions, the dosage was decreased to 15 units. He was transferred to another hospital before the treatment was completed "feeling the best that he had felt in 12 years." His average gain was $2\frac{1}{4}$ pounds a week.

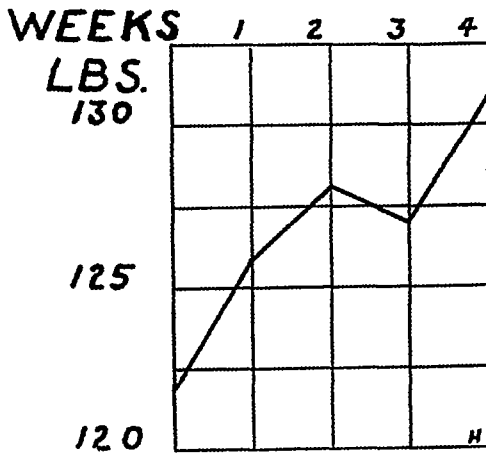


FIG 2 Weight curve of Case II

Case III A hotel manager, aged 52 years, entered the Marine Hospital because of weakness. His illness began one month before with an attack of influenza from which he did not seem to recover. He tired easily, had no appetite, and had lost 12 pounds in weight. Physical examination revealed anemia and malnutrition. Pulmonary tuberculosis was suspected but not found. The first month of observation revealed little or no change in his general condition with an increase in weight of one pound. Treatment with insulin was begun. His weight began to increase. The red blood cells soon increased almost a million, with a proportional increase in the hemoglobin. He became stronger with

greater endurance and was particularly grateful for his improvement. His average gain was over two pounds a week.

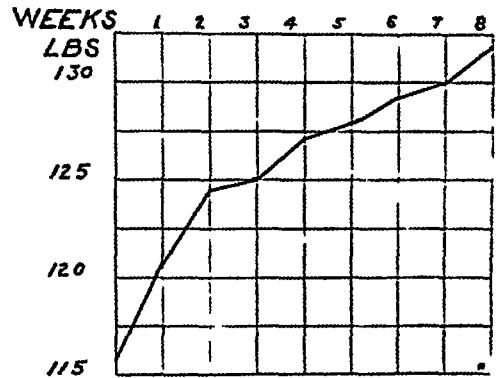


FIG 3 Weight curve in Case III

Case IV A salesman, aged 38 years, entered the Marine Hospital with a hypertrophic arthritis of 12 years duration. It particularly involved both knees and the spine. He was treated with analgesics and various physiotherapeutic procedures. Because of underweight and flabby musculature, insulin treatment was begun. His strength increased and his muscles became larger and firmer. While the insulin had no direct effect upon his arthritis, the patient's general sense of well-being was the best that he had experienced since its onset. Three months after the treatment was discontinued, he was holding the increased weight. His average gain was almost two pounds a week.

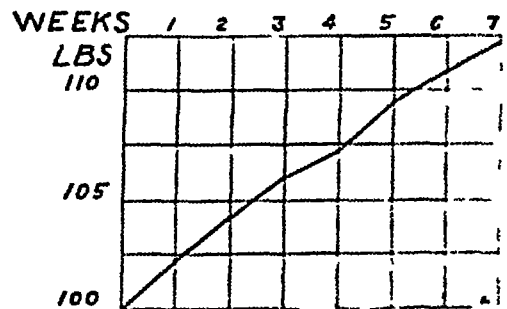


FIG 4 Weight curve in Case IV

REFERENCES

- ¹METZ, R D Insulin in malnutrition a preliminary report, Jr Am Med Assoc, 1931, xcvi, 1456-1460
- ²BANTING, F G, and BEST, C H The internal secretion of the pancreas, Jr Lab and Clin Med, 1922, vii, 251-266
- ³PITFIELD, R L Insulin in infantile inanition, New York Med Jr, 1923, cxviii, 217-218
- ⁴MARRIOTT, W McK The food requirement of malnourished infants with a note on the use of insulin, Jr Am Med Assoc, 1924, lxxxiii, 600-603
- ⁵BARBOUR, O The use of insulin in undernourished non-diabetic children, Arch Pediat, 1924, xli, 707-711
- ⁶FALTA Quoted by all German authors
- ⁷FRANK, E, and WAGNER, A Insulintherapie einschliesslich der Indikationen bei nicht diabetischen Erkrankungen Therapie in Einzeldarstellungen, 1931, Georg Thieme, Leipzig
- ⁸JACOBSEN, H Insulin "mastkur", Ugesk f laeger, 1930, xcii, 875-876 Abst Insulin in the treatment of undernutrition, Jr Am Med Assoc, 1930, xc, 1878
- ⁹CECCARELLI, D La terapia insulinica negli stati di dimagrimento consecutivi a colecistite calcolosa, Policlinico (sez prat), 1930, xxxvii, 1665-1672 Abst Insulin therapy in emaciation following calculous cholecystitis, Jr Am Med Assoc, 1931, xcvi, 646
- ¹⁰TOSCANO, C Le indicazioni extra-diabetiche della terapia insulinica, Policlinico (sez prat), 1931, xxxviii, 8-17
- ¹¹CARRODU, G, and GIUA, G L'insulina nel trattamento dei bambini ipotrofici, Riv di clin pediat, 1930, xxviii, 487-512
- ¹²AMICI, D L'insulinoterapia nell'atepsia della prima infanzia, Policlinico (sez prat), 1930, xxxvii, 1318-1320 Abst Insulin treatment in athrepsia in infants, Jr Am Med Assoc, 1930, xcvi, 1872
- ¹³ROI, G Quoted by Toscano¹⁰
- ¹⁴SHORT, J J Increasing weight with insulin, preliminary report, Jr Lab and Clin Med, 1929, xiv, 330-335
- ¹⁵GAMMON, G D, and TAPPY, W C Hypoglycemia, a clinical syndrome, etiology and treatment, report of case due to hyperinsulinism, Arch Int Med, 1931, xlvii, 829-854
- ¹⁶WILLIAMS, J R Allergic insulin reactions, Jr Am Med Assoc, 1930, xciv, 1112-1114
- ¹⁷EDITORIAL Insulin—a protein, Jr Am Med Assoc, 1931, xcvi, 1803-1804
- ¹⁸GRISHAW, W. H Allergic manifestation to insulin, Jr Am Med. Assoc, 1931, xcvi, 1885
- ¹⁹JEANNERET, R (Leysin) Une application pratique de la méthode de désensibilisation par les cuti-réactions répétées Urticaire à l'insuline, Rev méd de la Suisse Rom, 1929, xlix, 99-105 Abst Desensitization in insulin urticaria, Jr Am Med Assoc, 1929, xcii, 2197
- ²⁰FALTA Quoted by Depisch and Hasenohrl²¹
- ²¹DEPISCH, F, and HASENOHRL, R Zur Theorie der Gegenregulation in der Leber und im Gewebe, Klin Wchnschr, 1930, ix, 345-347 Abst Theory of counterregulation in the liver and in the tissues against insulin, Jr Am Med Assoc, 1930, xciv, 1452
- ²²CANNON, W B Linacre lecture on autonomic nervous system, an interpretation, Lancet, 1930, i, 1109-1115
- ²³COLUMBA, D L'insulinemia, nell'obesita e nella magrezza, Policlinico (sez prat), 1931, xxxviii, 219-222 Abst Insulinemia in obesity and emaciation, Jr Am Med Assoc, 1931, xcvi, 1837
- ²⁴FONSECA, F Magerkeit und Insulin Hyperinsulinismus, Arch f Verdauungskr, 1928, xlii, 362-377 Abst Emaciation and insulin, hyperinsulinism, Jr Am Med Assoc, 1928, xci, 362-363
- ²⁵HYMAN, H T, and KESSEL, L Studies of exophthalmic goitre and the involuntary nervous system, Jr Am Med Assoc, 1931, xcvi, 2014-2019
- ²⁶CORI, C F The influence of insulin and epinephrine on the fate of sugar in the animal body, The Harvey Lectures, 1927-28, Series 23, 76-114
- ²⁷MACFARLAN, J J R Lectures on the physiology of glycogen and the role of insulin and epinephrine in carbohydrate metabolism, Lancet, ii, 107-113

Carotinemia Associated with the Ingestion of Pumpkin

Report of a Case

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THE association of a yellow discoloration of certain areas of the skin with cases of diabetes mellitus was first brought to the attention of the scientific world by von Noorden in 1904. To this condition he gave the name xanthosis diabetica. Since then it has been variously designated as pseudoicterus,¹ hyperlipochromemia,² xanthemia,³ and carotinemia.⁴ This last term has been adopted by the majority of workers since Hess and Myers described the entity as a new clinical picture. Their work, and that of other investigators notably Palmer,⁵ has shown this condition to be associated with the ingestion of foods rich in carotin,* a yellow plant pigment. The especial retention of this pigment in the blood serum, epidermis, and sweat glands of certain diabetic and non-diabetic patients has attracted wide attention in the last decade.

The association of carotinemia with the ingestion of specific carotin bearing foods has been shown by Palmer.

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*Carotin = carotene.

Hess and Myers, Stannus,² Hashimoto,⁶ Boeck and Yater,³ Inlow⁷ and others. In the German literature Gragger⁸ has reported a single case of carotinemia associated with the eating of pumpkin. A search of the American literature, however, fails to reveal a single case report. Since the following case represents a carotinemia following the ingestion of large known amounts of pumpkin over a known period of time and its rapid disappearance on a carotin low diet, we thought it worthy of reporting.

REPORT OF CASE

Mr. D. T., aged 23, a student, was seen in the medical outpatient department as a return diabetic and tuberculous patient on April 22, 1931. The patient felt perfectly well but was somewhat apprehensive about a yellowish pigmentation of his skin which had developed within the last two months. This was the patient's third admission to the hospital.

The symptoms of diabetes mellitus were first noted in November, 1927. Diagnosis of this condition was made in September, 1928. A modified diet without insulin was ineffectual and he came to the University Hospital October 31, 1929 for treatment.

The diagnosis of diabetes mellitus was confirmed. Examination of his chest and his x-ray films showed a minimal border line tuberculosis. He was confined to the Tuberculous

Unit where he was also stabilized on a diet of 55 grams of proteins, 220 grams of fats, and 65 grams of carbohydrates with 45 units of insulin. The insulin was slowly decreased, after four months on the diet, until it could be dispensed with entirely. The carbohydrate of the diet was then slowly increased but as he gained an excess of weight it was necessary to reduce his calories. On May 15, 1930, he was discharged on a diet of 55 grams of proteins, 166 grams of fats, and 130 grams of carbohydrates.

He returned on September 15, 1930. His weight had been maintained at 160 pounds during this entire period. X-ray examination of the chest showed definite improvement. He had remained aglycosuric during this entire period so no change was made in his diet. He was advised not to return to active work but to gradually increase his activity at home.

From September 14, 1930, until April 22, 1931, a period of seven months, he had substituted baked pumpkin to the extent of 600 grams daily for his five per cent vegetables. It is of interest to know that he had partaken also of two eggs daily during this same time. His appetite for these foods remained undiminished at the time of his last admission on April 22, 1931.

Examination A generalized yellow tint of the skin and mucous membranes was found which was more accentuated in certain areas. This pigmentation was light picric acid yellow in some areas and extreme orange in others. This latter condition was present most noticeably in the palms of the hands. The lighter yellow pigmentation was seen on the forehead, soles of his feet, soft palate, nasolabial folds, inferior surface of the tongue, conjunctivae, dorsal surface of the hands, and lastly, patchy areas in the mid-abdomen and midlumbar regions. This pigmentation was everywhere diffuse and appeared more reddish yellow than in icterus. There was no tinting of the sclerae. No associated discomfort was present. Two small pea-sized lymph glands were palpated on either side of the neck in the region of the postcervical chain. The chest and heart examination was negative. Blood pressure was 124/76. The examination otherwise was essentially negative.

Laboratory Observations The blood count and differential smear were normal. The blood Kahn test was negative. Blood sugar was 104 mgm per 100 c.c. of blood. Blood bilirubin was 3.2 mgm per 1000 c.c. of blood. The blood serum appeared a cloudy ochre color. The urine showed nothing abnormal. An x-ray film of the chest showed no change from that taken on September 14, 1930. The test for carotin was positive. Using the method of Van den Bergh, Muller and Brockmeyer,⁹ the amount of carotin present was found to be equivalent to the color produced by 132 mgm of potassium dichromate in 100 c.c. of water. According to White's recent article on the estimation of carotin in the blood,¹⁰ this would be the color equivalent to 1.65 mgm of carotin in 100 c.c. of petroleum ether. After this determination the patient was placed on a carotin low diet for one month. On his return the yellow pigmentation had entirely disappeared and his blood carotin had fallen to 0.075 mgm of carotin per 100 c.c. of serum.

COMMENT

Carotinemia has been found in cases of diabetes mellitus, nephritis, and in adults and children whose diet contained large amounts of carotin containing foods. It is not a rare condition as may be seen by a study of almost any of the recent reviews of the literature.¹¹ The case reported here is interesting because the carotinemia resulted from the ingestion of a known amount of carotin-rich food over a definite and long period of time in a patient whose diagnosis was known. It also represents an extreme case of carotinemia since White¹⁰ states that "our experience has shown that even the most pronounced cases of carotinemia have values which lie in the lower segment of the graph"—namely less than 0.750 milligrams of carotin per 100 c.c. of serum. Our case had more than twice that amount. Furth-

ermore, it demonstrates how quickly the blood carotin falls to a normal level after the patient had been placed on a carotin low diet. White¹⁰ has shown in 18 normal individuals that a blood carotin mean of 0.063 mgm per 100 c.c. of serum was present. Our figures, in 17 normal people, show a blood carotin mean of 0.106 mgm per 100 c.c. of serum. The case reported here returned approximately to this level in one month.

SUMMARY

1 A case of carotinemia associated with the ingestion of pumpkin is presented.

2 The areas pigmented were the palms of the hands, soles of the feet, forehead, nasolabial folds, lips, soft palate, inferior surface of the tongue, conjunctivae, abdomen and lumbar regions.

3 The case is illustrative of the extent to which carotinemia can develop due to the ingestion of a food rich in carotin content over a period of seven months.

4 The blood carotin content at the height of the carotinemia was found to be 1.65 mgm per 100 c.c. of serum and one month later with a carotin low diet it was 0.075 mgm per 100 c.c. of serum.

REFERENCES

- ¹STOELTZNER, W. Pseudoikterus nach Mohrrubengenuss, *München med Wchnschr*, 1919, *lxvi*, 419.
- ²STANNUS, H. S. Hyperlipochromia, carotinemia, xanthosis cutis, *Internat Clinics*, 1929, *i*, 146-163.
- ³BOECK, W. C., and YATER, W. M. Xanthemia and xanthosis (carotinemia), clinical study, *Jr Lab and Clin Med*, 1929, *xiv*, 1129-1143.
- ⁴HESS, A. F., and MYERS, V. C. Carotinemia new clinical picture, *Jr Am Med Assoc*, 1919, *lxviii*, 1743-1745.
- ⁵PALMER, L. S., and ECKLES, C. H. Carotin, the principal natural yellow pigment of milk fat, its relation to plant carotin and the carotin of the body fat, corpus luteum and blood serum. III, The yellow lipochrome of blood serum, *Jr Biol Chem*, 1914, *xii*, 223-236.
- ⁶HASHIMOTO, H. Carotinoid pigmentation of skin resulting from vegetarian diet, *Jr Am Med Assoc*, 1922, *lxviii*, 1111-1112.
- ⁷TALOW, H. H. Possible carotinemia from eating papaw, *Jr Am Med Assoc*, 1929, *xciii*, 1085.
- ⁸GRAGGER, E. Über einen Fall von Xanthiasis cutis Baelz, *Dermat Wchnschr*, 1929, *lxviii*, 716-718.
- ⁹VAN DEN BERGH, HYMAN, S., MILLER, P., and BROENFELDER, J. Das lipochrome Pigment in Blutserum und Organen, Xanthosis, Hyperlipochromämie. *Biochem Zeitschr*, 1920, *cvi*, 279-303.
- ¹⁰WHITE, F. D. Estimation of serum carotin, *Jr Lab and Clin Med*, 1931, *xvii*, 53-59.
- ¹¹LEVIN, O. L., and SHARPS, S. H. Carotinemia resulting from restricted diet as observed in dermatologic practice 1931, *xcvi*, 2190-2193.

A Comparison of Blood Pressure in Men and Women

A Statistical Study of 5,540 Individuals

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A STUDY has been made of the routine blood pressure reading of all individuals admitted to the medical division of the out-patient department of the University of Minnesota Hospital. These records cover the three year period from December, 1926, to December, 1929. There are in this series 5,540 individuals, 3,258 women and 2,282 men. The readings have been classified by decades for systolic and diastolic pressures, and a comparative study has been made of blood pressures in men and women.

LIFE INSURANCE STATISTICS

There have been a number of statistical studies of blood pressure. The larger groups have been in accepted life insurance risks such as those of Goepp,¹ MacKenzie,² Fisher,³ Hunter,⁴ and Symonds.⁵ For the most part this material consists of men under 50 years of age.

The two largest series of cases are those of Hunter⁴ and of Symonds,⁵ and these show very much the same

averages of systolic pressures for the corresponding age groups. Hunter's series represents about a quarter of a million individuals, and Symonds has a group of 150,419 men and 11,937 women. Symonds noted that under 40 years of age, the systolic pressure of women is one or two mm Hg less than that of men, and that after 49 years of age it equals or exceeds that of men by one or two mm Hg. Adams⁶ cited figures of G. W. Exton, director of laboratories and longevity service of the Prudential Life Insurance Company. He has submitted a record of 5,727 blood pressure readings from accepted and rejected risks in men and women. Unfortunately, average pressures for sex and age group are not given but the percentage of systolic pressures exceeding 150 mm Hg and of diastolic pressures exceeding 100 mm Hg are given. This shows a marked relative increased incidence in the occurrence of systolic and diastolic pressures at higher levels in women over thirty years of age.

Life insurance tables are of great practical value to their respective companies. These are largely made up of accepted risks, and represent much the same figures as our clinical tables of

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averages, if we eliminate nearly all readings of 150 mm Hg and over. Even in those tables including rejected risks, it must be remembered that presumably healthy individuals apply for life insurance. The financial factor also brings some errors into insurance figures.

BLOOD PRESSURE IN CHILDREN

Blood pressure studies in children up to 17 years of age have been made by Judson and Nicholson,⁷ and Faber and James.⁸ They have found the average blood pressure by age groups to be about the same for boys and girls.

BLOOD PRESSURE IN COLLEGE STUDENTS

There have been rather extensive studies of young college students as in Alvarez's^{9, 10} series of University of California freshmen and in the series of Diehl and Sutherland¹¹ at the University of Minnesota. From both sources it seems evident that the average systolic pressure in men from 17 to 30 years of age is higher than for women of similar age. Alvarez recorded as high as 22 per cent of the young men with a systolic pressure exceeding 140 mm Hg and only 2 per cent of the young women exceeding that pressure. These were single readings, and with the men were taken after a shower bath. Diehl and Sutherland¹¹ found 16 per cent of the men examined in 1922 to have a systolic pressure exceeding 140 mm; but on taking precautions to eliminate nervousness and excitement they found 9 per cent over 140 mm in their 1923 and 1924 groups. On reexamination

they found only 1.6 per cent of the total group with a persistent pressure of 140 mm Hg or more. The significance of a transient elevation of blood pressure in young men has not been determined. Diehl¹² has since studied systolic blood pressure in 976 young women in whom he has found a mean pressure of 116.70 mm Hg as compared with a mean of 122.7 in the young men. In the young women 7 per cent exceeded 140 mm Hg as compared with 9 per cent of the young men.

BLOOD PRESSURE IN MEN AND WOMEN

A comprehensive study of blood pressure has been made by Saller¹³ in a group of over 4,000 individuals examined at the Universitäts Klinik at Kiel. In his group there are 2,468 men and 1,743 women, ranging in age from 3 to 89 years. He has shown that the average systolic pressure tends to be slightly higher in men than women under 36 years of age. In all age groups beyond 36 years there is a marked increase in the systolic pressure of women as compared with men. As an example it is noted that in the men from 51 to 56 years of age the average systolic pressure is between 126 and 127 mm Hg, while for the women of the same age group the average systolic pressure is 148 mm Hg. Similarly there is noted a greater range of variability in the pressures of the women as compared with those of the men in similar age groups over 36 years of age. He has also shown a tendency for the average diastolic blood pressure of women to exceed that of the men. In the groups over 50 years

of age diastolic pressure is about 10 mm higher in the women than in the men of similar age groups

Gelman¹⁴ has presented a study of blood pressure in 3,761 individuals. This group was largely composed of presumably normal working people, 2,641 men and 1,120 women. In his series he found more men than women with systolic pressures exceeding 141 mm, however, there were very few individuals over 50 years of age in his series. There were only 35 women over that age. Under 30 years he found many more men than women with pressure exceeding 141 mm. In his group from 30 to 39 years of age, he found 11 per cent of the women and 6 per cent of the men with systolic pressures exceeding that figure. In his group from 40 to 49 years he found 19 per cent of the women and 15 per cent of the men with systolic pressures exceeding 141 mm. Gelman¹⁴ classified blood pressure in relation to age and occupation and showed strikingly increased incidence in the percentage of hard laborers showing systolic pressures exceeding 141 mm, and this was particularly true of the foundry workers.

Alvarez⁹ has recorded systolic blood pressure readings in 1,000 office patients showing pressures in the men higher than women under 40 years of age, and definitely higher in the women after 40 years of age.

Gager¹² has recorded pressures in 2,000 consecutive individuals seen at the Cornell Clinic. These consisted of 1,000 men and 1,000 women. In individuals under 30 years of age he found more men than women with systolic pressures of 140 mm or greater. In

the group from 30 to 39 he found the incidence much the same. In the groups from 40 to 59 years of age he found a markedly increased incidence of women over men with pressures of 150 mm and greater. In the groups of sixty years and over he found about the same incidence, however, the number of individuals in the latter groups was not sufficient to allow for error. In considering diastolic blood pressure Gager found that the sex-age distribution of individuals exceeding 90 mm was relatively much the same as for systolic pressure.

Riseman and Weiss¹⁶ recorded the incidence with which the diagnosis of hypertension was made in the wards and the medical out-patient department of the Boston City Hospital. The blood pressure readings were found to be 160 mm Hg or over in 91.6 per cent of the out-patient group on whom the diagnosis was made. In the group of ward patients 95.3 per cent had a systolic pressure of 160 mm or greater. It is of interest that in a group of 28,906 out-patients a diagnosis of hypertension was made in 1,620 instances and that on a basis of corrected sex incidence 29.5 per cent of the patients were men and 70.5 per cent of the patients were women. This relative incidence was about the same in a group of hospital patients.

BLOOD PRESSURE IN OLDER INDIVIDUALS

Wildt¹⁷ has reported the blood pressure readings of 248 chronic hospital patients ranging from 60 to 89 years of age. There was a definite trend for the average systolic and diastolic pres-

tures of the women to be greater than those of the men under 80 years of age. From 80 to 89 years, it was about the same in the small group of 14 individuals. He also showed a tendency for the average blood pressure to increase with advancing age prior to 90 years. Four individuals over 90 years of age showed a marked drop in the average systolic and diastolic pressures.

Bowes¹⁸ has recorded pressures in a group of 150 individuals from 65 to 95 years of age. He, too, showed a definite increase in the average systolic pressure of the women as compared with the men and as in Wildt's group showed a drop in the pressure of seven individuals over 90 years of age.

Richter¹⁹ in a study of blood pressure of 165 individuals from 60 to 89 years of age found 83 with a systolic pressure of 150 mm Hg or over.

Davis²⁰ has reported blood pressure in 50 white males over 75 years of age at the Johns Hopkins Hospital and has cited records of 102 white men over 75 years from the Royal Hospital, Chelsea. The systolic averages are about the same. Fifty per cent of the Hopkins group have a pressure exceeding 150 mm, with a mean systolic pressure of 158.3 ± 3.2 mm.

UNIVERSITY OF MINNESOTA OUT-PATIENT RECORDS

The patients admitted to the outpatient department are largely from the lower and lower middle classes. All individuals are interviewed as to financial eligibility before admission.

The charges are nominal and in some cases no charge whatever is made. The patients are from both the city and country and are largely laborers, farmers, housewives, and working women. Many had no medical complaint but were examined as a routine procedure. These patients are ambulant and many have minor complaints or have physical examinations as a routine procedure preliminary to tonsillectomy or hospital employment. A very small percentage come in because of symptoms suggesting hypertension. All patients admitted to the medical clinic were included and routine blood pressures taken as a part of each patient's study. The only cases excluded from the list were the clearcut cases of glomerulonephritis and aortic insufficiency. It has been interesting to notice the infrequency with which a diagnosis of true nephritis has been made. Consideration has not been given to obesity, although it is well recognized that the overweight individuals tend to have a higher pressure.

TECHNIC EMPLOYED

The blood pressure in all instances was taken with mercury manometers and by the auscultatory method. The diastolic pressure has been considered as the fourth phase. Most of the readings were taken in the sitting position. Patients had been sitting from thirty minutes to two hours prior to the examination and the blood pressure was taken after the history and near the end of the examination. In this way the factor of physical exertion was eliminated and the element of excitement reduced to a minimum.

STATISTICAL ANALYSIS

An analysis has been made of the blood pressures of 5,540 individuals, 2,282 men and 3,258 women. These have been considered in two groups, the total group and a group consisting of systolic pressures of 150 mm and over, and diastolic pressures of 100 mm and over. There are certain tendencies to error in any consideration of average blood pressure. One is the frequency with which readings are made on the divisions of ten and another is that manometer scales are marked off at two millimeter intervals.

(a) The means are arithmetic averages based on 5 mm groupings of blood pressure.

(b) The standard deviations of the distribution are the root mean square deviations of these groups about the mean.

(c) The probable error of the mean is the standard deviation divided by the square root of the number of cases.

(d) The probable error of the standard deviation is the standard deviation of the distribution divided by the square root of twice the number of cases.

(e) The coefficient of variation represents the standard deviation of the distribution expressed in percentage of the mean.

(f) The probable error of a difference is the square root of the sum of the squares of the probable errors of the constants between which the difference is taken.

(g) A difference is regarded as significant if its ratio to its probable error is three or more.

(h) A measure of difference is given by Pearson's χ^2 test (Pearson, Karl, on the test of Goodness of Fit, *Biometrika*, 1922-23, xiv, 186).

(i) P gives the probability that a given χ^2 would occur in a normal variation of one sample.

Figures 1 and 2 show for the men and for the women separately the frequency distribution of systolic blood

pressure in percentage of their respective age groups. The charts have been constructed by grouping the readings in intervals of 5 mm Hg. The charts further show a practically symmetrical distribution of the readings within the three lowest age groups, as contrasted with a skewness of the material in the fourth and fifth groups and with a more diffuse spread of readings within the sixth and seventh groups.

Table I shows the mean values, standard deviations and coefficients of variability of the systolic pressure for the entire material, arranged according to sex and according to age, the latter expressed in decades (except for the age group 15 to 19). Both for men and for women there is a steady rise of the mean pressure from one age group to the other. From the ages of 15 to 39 the rise is slight. In the fifth decade (40 to 49) there is for the women a sudden rise of 14 mm, being just twice the rise in the preceding decade. This rise brings the women 12 mm above the men, a difference which is not only maintained but slightly increased during the following decades. A sudden rise corresponding to the one just described occurs, to be sure, among the men; but one decade later than in the women. During this decade, the sixth, the mean pressure for the women has again risen. Thus, as was just stated, the mean pressure of the men never catches up with that of the women.

This, in a way, is the main finding brought out in the present study, and the following discussion serves further to elucidate this point. Attention is called to the fact that as this sudden break in the blood pressure curve

takes place, in the fifth decade for the women and in the sixth for the men, it is not only the mathematical mean that changes, but also the standard deviation and particularly the coefficient of variability, the latter becoming twice what it was in the first age groups. The coefficients of variability

whether this difference is significant or not. Such testing is also necessary for the larger differences already discussed. Applying the commonly accepted requirement that the ratio between the difference of the means and the probable error of the difference shall not be less than 3, it becomes

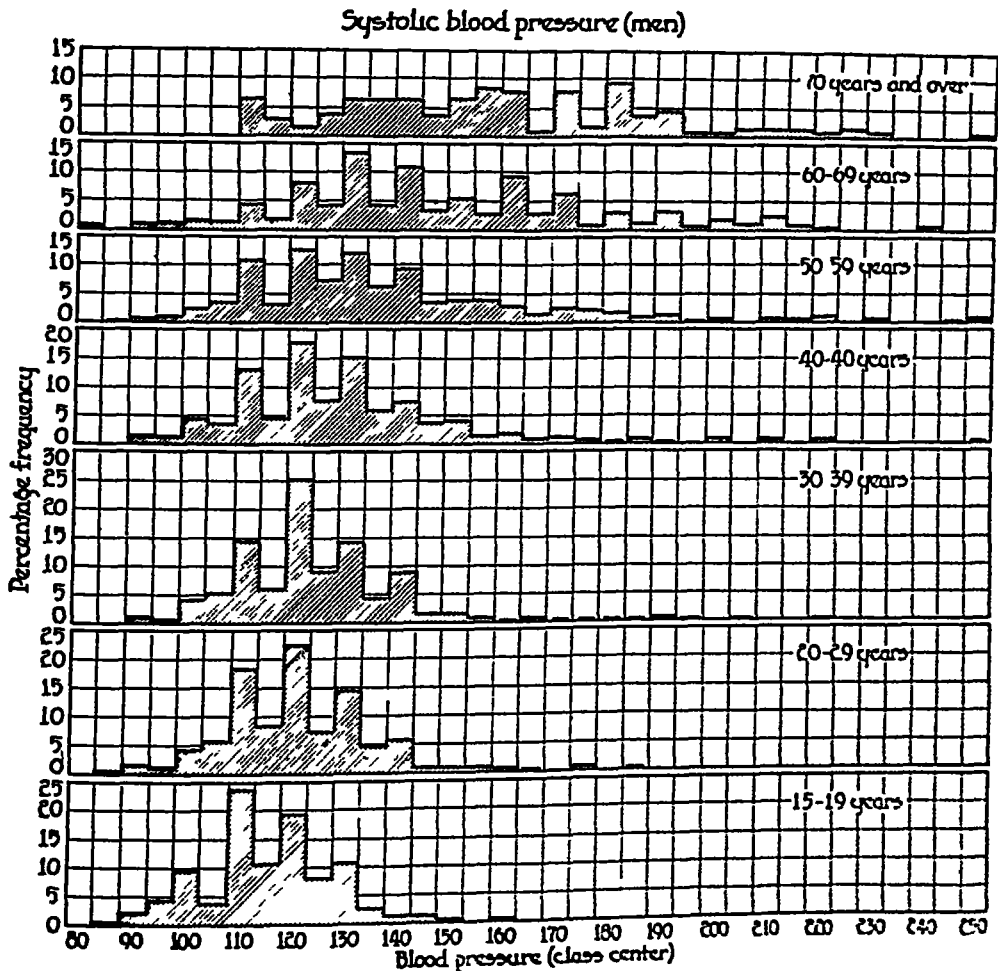


FIG 1 Percentage frequency distribution of systolic blood pressure by 5 mm groups for men

both for men and for women already show a definite rise in the decade preceding that characterized by the sudden rise in mean systolic pressure. It also is shown in table I that in the age group 30 to 39 the mean pressure for the women is already slightly

higher than the corresponding figure for the men, 2.88 mm to be exact. Without a mathematical test it is impossible to have any opinion as to whether this difference is significant or not. Such testing is also necessary for the larger differences previously discussed. Applying the commonly accepted requirement that the ratio between the difference of the means and the probable error of the difference shall not be less than 3, it becomes

(the ratios for the age groups 40 to 49 and 50 to 59 being 12.05 and 11.24 respectively), and second, that even the small elevation of the mean pressure for the women between 30 to 39 above the corresponding mean for the men is of mathematical significance (the ratio being 4.64)

In order better to understand the meaning and significance of the

changes in the mean pressure in men and women, a brief discussion seems useful before the presentation of any further tables. As previously stated cause of the gradual elevation of the mean pressures. There is first the possibility that the pressure rises slightly in the population as a whole, further, it might be that the elevations of the means are caused by a certain

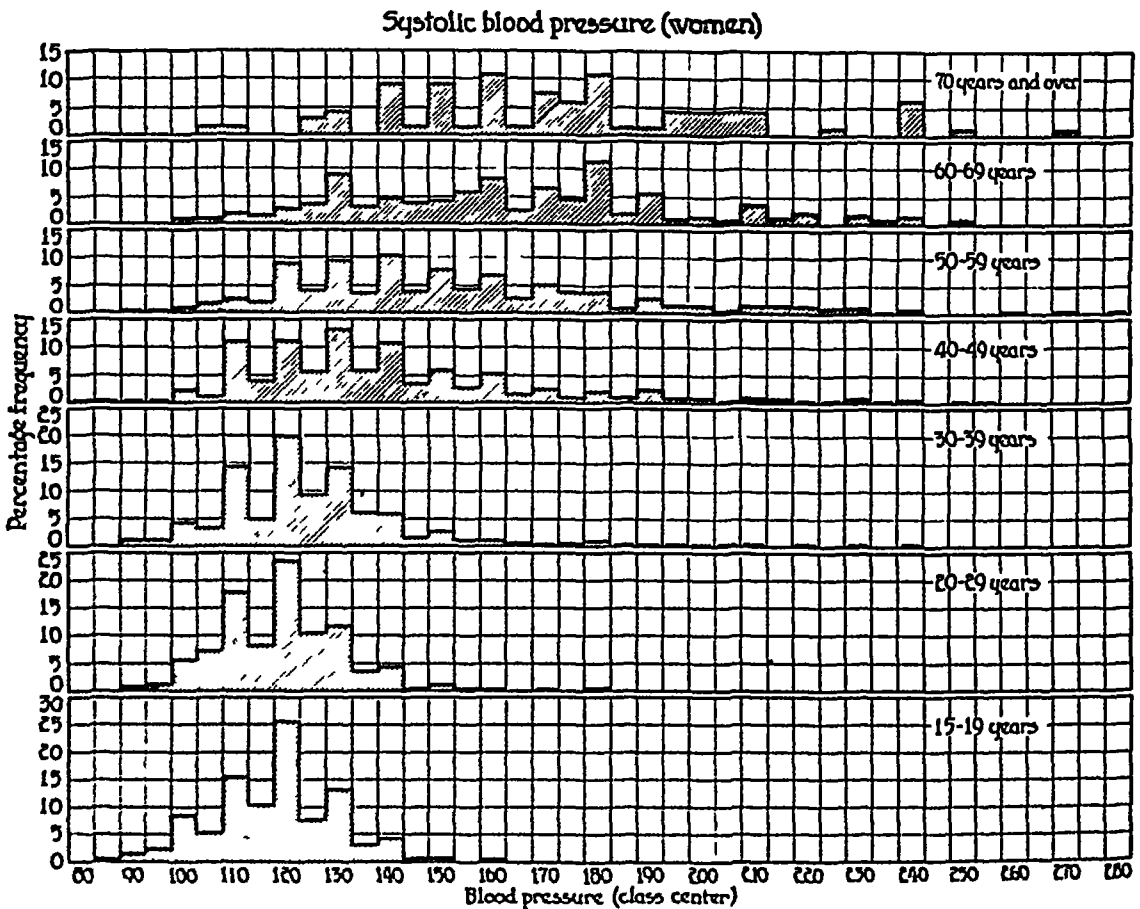


FIG. 2 Percentage frequency distribution of systolic blood pressure by 5 mm groups for women

the material under analysis consists of a practically unselected out-patient population, derived from both city and rural districts—only instances of aortic insufficiency and definite chronic glomerulonephritis having been eliminated. One might conceive of two different phenomena as the possible

number of definite hypertension mixed in with a large group of normal people, possessing pressures the same as in the groups below 30 for the women or below 40 for the men. Table VI shows that a noticeable number of cases of moderate elevation of blood pressure start to appear 10

TABLE I
Systolic Blood Pressure in the Total Material

AGE GROUP YEARS	NO OF CASES	MEAN PRESSURE P F	STANDARD DEVIATION P F	COEFF VARIATION
MEN				
15-19	135	115.67 \pm 0.74	12.81 \pm 0.52	11.07
20-29	477	120.24 \pm 0.42	13.63 \pm 0.30	11.34
30-39	495	122.95 \pm 0.40	13.28 \pm 0.28	10.80
40-49	437	127.26 \pm 0.68	21.05 \pm 0.48	16.54
50-59	365	137.30 \pm 1.02	29.06 \pm 0.72	21.16
60-69	247	146.90 \pm 1.25	29.15 \pm 0.88	19.84
70 and over	126	158.10 \pm 1.79	29.86 \pm 1.27	18.89
WOMEN				
15-19	285	117.93 \pm 0.47	11.81 \pm 0.33	10.01
20-29	731	119.55 \pm 0.55	12.94 \pm 0.23	10.82
30-39	786	125.83 \pm 0.48	19.79 \pm 0.34	15.73
40-49	636	139.43 \pm 0.75	27.92 \pm 0.53	20.02
50-59	513	152.92 \pm 0.96	32.04 \pm 0.68	20.95
60-69	241	163.92 \pm 1.43	32.97 \pm 1.01	20.11
70 and over	66	174.09 \pm 2.83	34.06 \pm 2.00	19.56

years earlier among the women than among the men (30 to 39 group for women vs 40 to 49 group for men). This incidence of rather moderate elevation of systolic pressure increases rapidly among the women but more slowly among the men, as seen in table VI. Thus in regard to frequency of elevated systolic pressure, the women in the age group 40 to 49 are as badly off as the men 20 years later. This is well brought out for pressures above 150 and above 160 mm Hg.

A test of significance is made for the relative incidence of systolic pressures in men and women exceeding 150 mm Hg (table VII). Pearson's χ^2 test (h) gives a measure of difference which is interpreted directly on a probability scale. $P(1)$ measures the chance that a given difference would occur in a normal variation. Thus in table VII $P = 0.8$ corresponding to a $\chi^2 = 0.1432$ in the 15 to 19 age groups for systolic pressure, meaning that there are eight chances in

ten that men and women in the given sample are not differentiated with respect to incidence of systolic blood pressure over 150 mm or that there are two chances in ten that they are so differentiated. The P 's (table VII) indicate a small probability of sex difference for individuals under 30 years of age for systolic pressure. For the age groups over 30 years the probabilities are indicative that women have a significantly greater incidence of systolic pressure exceeding 150 mm.

Whether the elevated systolic pressures among women are of greater degree than among men is tested in table II which includes all individuals with a pressure of 150 mm Hg or more. If the means for the women are compared with the means for men age group for age group, and the differences tested as to significance in the usual way, no significant difference between these two sets of figures is found to exist.

Table III shows the mean values

TABLE II
Systolic Blood Pressure of Individuals with Pressure of 150 mm. Hg or More

AGE GROUP YEARS	NO OF CASES	MEAN PRESSURE P. E	STANDARD DEVIATION P. E	COEFF VARIATION
MEN				
30-39	22	169.36 \pm 2.45	17.05 \pm 1.73	10.07
40-49	52	169.36 \pm 2.07	22.19 \pm 1.46	13.11
50-59	91	177.42 \pm 1.89	26.86 \pm 1.34	15.14
60-69	103	174.89 \pm 1.36	20.60 \pm 0.96	11.78
70 and over	77	176.63 \pm 1.62	21.18 \pm 1.15	11.97
WOMEN				
30-39	73	170.79 \pm 1.79	22.75 \pm 1.27	13.32
40-49	177	175.20 \pm 1.20	23.83 \pm 0.85	13.60
50-59	249	177.88 \pm 1.12	26.22 \pm 0.79	14.74
60-69	156	180.33 \pm 1.97	36.62 \pm 1.39	20.31
70 and over	52	185.88 \pm 2.72	29.12 \pm 1.92	15.67

TABLE III
Diastolic Blood Pressure in the Total Material

AGE GROUP YEARS	NO OF CASES	MEAN PRESSURE P. E	STANDARD DEVIATION P. E	COEFF VARIATION
MEN				
15-19	135	73.37 \pm 0.59	10.20 \pm 0.42	13.90
20-29	474	77.38 \pm 0.33	10.81 \pm 0.24	13.97
30-39	495	79.90 \pm 0.34	11.10 \pm 0.24	13.89
40-49	437	81.62 \pm 0.44	13.48 \pm 0.31	16.52
50-59	365	85.20 \pm 0.56	15.93 \pm 0.40	18.70
60-69	247	87.83 \pm 0.74	17.19 \pm 0.52	19.57
70 and over	126	87.86 \pm 1.00	16.67 \pm 0.71	18.97
WOMEN				
15-19	285	74.88 \pm 0.39	9.71 \pm 0.27	12.97
20-29	731	77.24 \pm 0.25	9.94 \pm 0.18	12.87
30-39	786	80.16 \pm 0.28	11.72 \pm 0.20	14.62
40-49	636	85.63 \pm 0.38	14.11 \pm 0.27	16.48
50-59	513	89.60 \pm 0.48	16.21 \pm 0.34	18.09
60-69	241	92.82 \pm 0.76	17.54 \pm 0.54	18.90
70 and over	66	94.85 \pm 1.60	19.23 \pm 1.13	20.27

standard deviations, and coefficients of variability of the diastolic pressure for the entire material arranged according to sex and age as in the systolic groups (See also figures 3 and 4) The diastolic pressure being of lesser magnitude fails to show as striking difference as the systolic. There is, however, a steady rise in the mean pressure by decades for both men and women. The pressures are about the

same in men and women until the fifth decade (40 to 49). At this point the women show abrupt rise, their mean pressure exceeding that of the men by 4 mm. In the sixth decade the men show similar elevation of the mean diastolic pressure. There is a continued rise for the women so that the mean diastolic pressure for the women is higher than for the men in all decades of life over 40 years. The

standard deviations and the coefficients of variability rise the same as for systolic pressure. The difference between the means for the women and the men are statistically significant in all age groups over 40 years, as shown in table V. The significance is definite though of lesser magnitude than for the systolic pressures.

Prior to 40 years of age about the same percentage of men and women

have diastolic pressures exceeding 90 and 100 mm (as shown in table VI). After 40 years there is a higher percentage of women than men with such pressures, the percentage of diastolic pressures at higher levels being about the same for the women as for the men one decade older. Pearson's test of significance (table VII) has been applied to the comparative incidence of diastolic pressures for men and

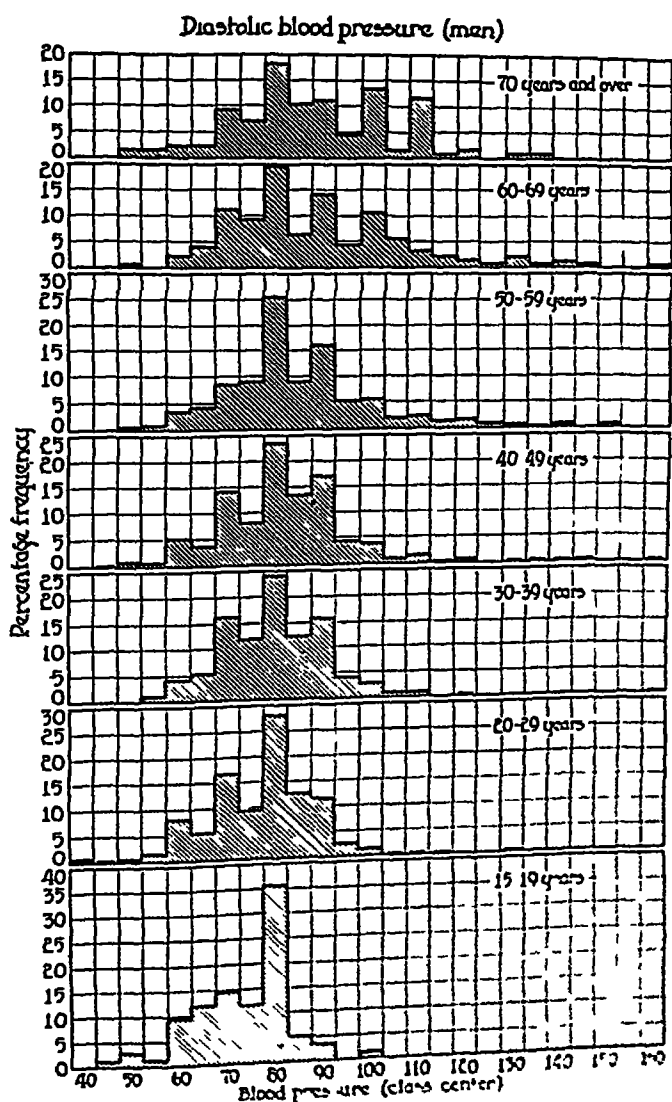


FIG 3 Percentage frequency distribution of diastolic blood pressure by 5 mm pressure classes for men

TABLE IV
Diastolic Blood Pressure of Individuals with Pressure of 100 mm Hg or More

AGE GROUP YEARS	NO OF CASES	MEAN PRESSURE P E	STANDARD DEVIATION P E	COEFF VARIATION
MEN				
30-39	18	107.72 ± 2.18	13.76 ± 1.54	12.78
40-49	29	112.89 ± 1.90	15.20 ± 1.34	13.46
50-59	55	113.34 ± 1.25	13.81 ± 0.88	12.19
60-69	58	111.79 ± 1.18	13.43 ± 0.84	12.02
70 and over	36	108.19 ± 1.09	9.75 ± 1.09	9.02
WOMEN				
30-39	43	109.93 ± 1.30	12.64 ± 0.91	11.50
40-49	98	110.00 ± 0.71	10.48 ± 0.50	9.54
50-59	116	112.89 ± 0.81	12.95 ± 0.57	11.47
60-69	76	112.51 ± 1.15	14.90 ± 0.81	13.24
70 and over	28	111.35 ± 1.88	14.76 ± 1.33	13.26

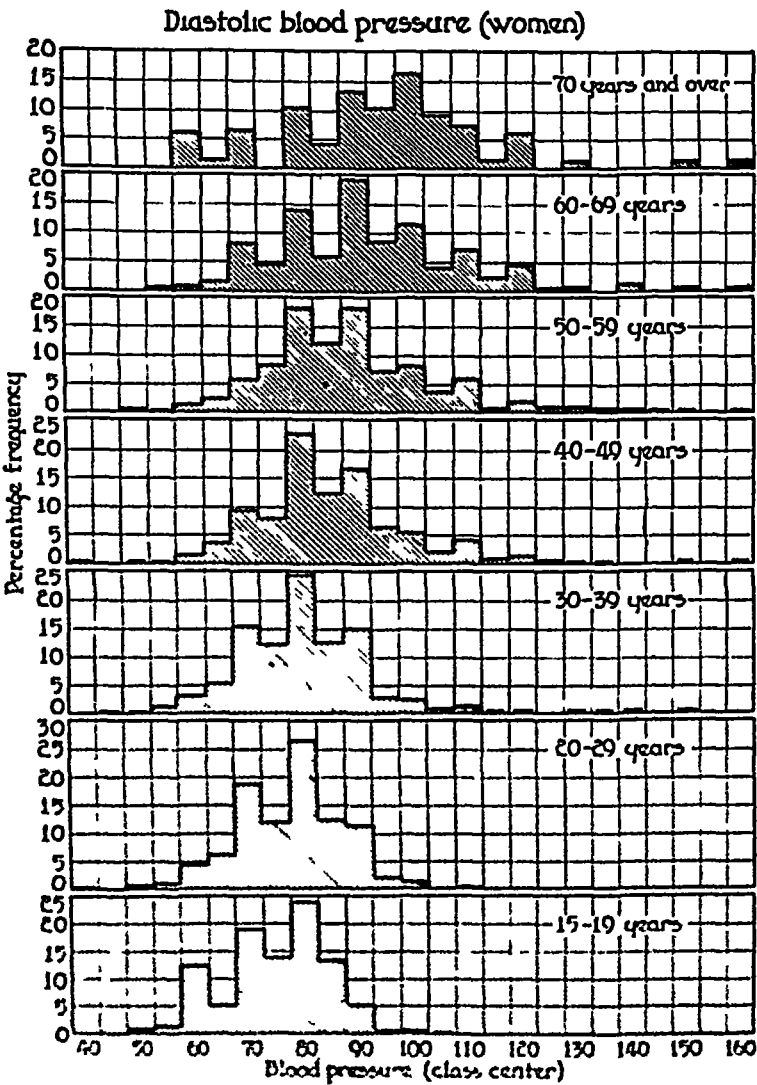


Fig. 4. Percentage frequency distribution of diastolic blood pressure by 5 mm groups for women.

women exceeding 100 mm For the age groups higher than forty years the P's indicate a definite probability that the women have a significantly higher percentage of diastolic pressures exceeding 100 mm Hg

For individuals with diastolic pressures in excess of 100 mm the mean pressures are about the same for corresponding age groups of men and women (table IV) There are no significant differences (table V)

DISCUSSION

The preceding analysis is undoubtedly on a somewhat selected group of individuals as it includes all those admitted to our medical out-patient division Some subsequent studies have convinced me that the incidence of higher pressures is somewhat higher than that of the population as a whole The sex comparison however seems to be on an unselected basis

The analysis has revealed that

women exhibit an elevated systolic blood pressure more frequently than men, that this difference is noticeable already in the age group 30 to 39 and becomes more marked in the following decade, during which as many instances of elevated blood pressure are to be found among the women as one finds among the men who are 20 years older Among the individuals who show a systolic pressure of 150 mm Hg or thereabove, men and women do not seem to differ in any significant way as to the degree of the elevation of the pressure

We must remember that this is a statistical study of blood pressure and not a clinical study of hypertension consequently no record of the incidence of concomitant signs of hypertension (enlargement of the heart, retinal arteriosclerosis, etc) among the individuals exhibiting a pressure of 150 mm or more, has been worked up for inclusion in this paper Neither has

TABLE V
Sex Differences by Decades for Blood Pressure in Total and Elevated Samples

AGE GROUP YEARS	TOTAL SAMPLE			ELEVATED SAMPLE		
	DIFF (MM) WOMEN-MEN	P E DIFF (MM)	DIFF	DIFF (MM) WOMEN-MEN	P E DIFF (MM)	DIFF
			P E DIFF			P E DIFF
SYSTOLIC BLOOD PRESSURE						
15-19	2.26	0.88	2.57			
20-29	0.69	0.69	1.00			
30-39	2.88	0.62	4.64	1.43	3.04	0.47
40-49	12.17	1.01	12.05	5.84	2.40	2.43
50-59	15.62	1.39	11.24	0.46	2.21	0.21
60-69	17.02	1.89	9.00	5.44	2.40	2.26
70 and over	15.99	3.34	4.79	9.25	3.17	2.91
DIASTOLIC BLOOD PRESSURE						
15-19	1.51	0.71	2.12			
20-29	0.14	0.41	0.34			
30-39	0.26	0.44	0.50	2.71	2.55	0.87
40-49	4.01	0.58	6.91	2.00	2.03	1.42
50-59	4.40	0.74	5.94	0.45	1.50	0.70
60-69	4.99	1.06	4.71	0.72	1.65	0.44
70 and over	6.09	1.88	3.72	3.16	2.18	1.45

TABLE VI
The Percentage of Cases Above Certain Blood Pressure Levels for
Men and Women in the Total Out-Patient Group

BLOOD PRESSURE	15-19 YEARS		20-29 YEARS		30-39 YEARS		40-49 YEARS*		50-59 YEARS		60-69 YEARS		70 YEARS AND OVER	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
SYSTOLIC BLOOD PRESSURE														
130 mm	4.64	6.31	9.86	8.48	14.74	18.21	23.36	55.67	39.73	65.16	57.47	75.95	72.22	89.39
150 mm	1.18	1.05	2.94	3.01	4.84	10.33	12.38	40.89	26.31	50.50	42.88	66.82	61.90	78.78
170 mm	0.71	0.34	1.26	1.10	2.61	5.87	7.12	32.24	18.63	38.03	34.38	56.45	46.82	68.17
180 mm			0.21	0.41	1.40	3.07	2.99	21.55	8.50	19.22	15.36	34.04	28.56	42.40
200 mm					0.40	1.30	1.84	15.42	4.66	9.52	7.68	13.71	9.52	24.21
DIASTOLIC BLOOD PRESSURE														
90 mm	5.18	7.36	16.44	15.60	24.85	24.03	29.99	40.26	38.34	50.70	46.15	62.66	46.83	69.73
100 mm	1.18	1.05	2.10	1.92	4.85	6.09	8.48	16.83	16.70	24.17	27.12	34.45	30.96	45.48

the constancy of the elevation of the blood pressure been studied in detail Caution must therefore be taken in discussing to what extent the difference between men and women, so clearly brought out by the analysis, represents a preponderance of chronic hypertension or only a greater lability of the systolic pressure among women That the labile character of normal and abnormal blood pressures alike constitutes the chief limitation of the significance of single as well as of serial blood pressure readings is by now well recognized and has been emphasized by O'Hare,²¹ Mosenthal,²² Kylin,²³ Ayman²⁴ and others If a greater blood pressure lability among women is the explanation for the difference brought out in this study, then it becomes necessary to introduce a new assumption, namely, the development of such an increased lability among women above the age of 29, since no trace of such a sex difference can be noticed in the two age groups below 30, where not only the mean pressure but also the standard deviations are the same for both sexes The writer does indeed hesitate to introduce such a new concept

There exist certain indications that chronic hypertension in its course and outcome behaves as a milder disease among women than among men In the out-patient service of the University Hospital where there is little difference between the number of men and women above the age of 50, there are a number of women with marked elevation of pressures, but very few men who have been followed over a period of several years Blackford, Bowers, and Baker, in a follow-up

TABLE VII
Comparative Incidence for Men and Women of Systolic Blood Pressure
of 150 mm and Over, and Diastolic Blood Pressure
of 100 mm and Over

AGE GROUP YEARS	SYSTOLIC BLOOD PRESSURE		DIASTOLIC BLOOD PRESSURE	
	χ^2	P	χ^2	P
15-19	0 1432	0 8000	0 5826	0 8000
20-29	0 2985	0 8000	0 0027	0 8000
30-39	10 3746	0 0160	2 2535	0 5266
40-49	39 1598	0 0000	19 1031	0 0003
50-59	61 9519	0 0000	11 0200	0 0117
60-69	25 9766	0 0000	3 9719	0 2651
70 and over	6 1389	0 1061	3 7403	0 2953

study of patients with systolic pressures of 175 mm Hg or more found 65 per cent to be women, while their general group did not show any such sex preponderance. Their patients were followed from five and a half to eleven years and showed during this time a mortality of 70 per cent for men and 39 per cent for the women. The average length of life, after the diagnosis had been made, was longer for the women than for the men. Riesman²⁶ likewise comments upon the relatively benign nature of hypertension in women.

Applying these facts to our problem, a more benign course of hypertension among women would account for a greater accumulation of high blood pressures among women of more advanced age, probably starting at about 50 years, than among men. And such are indeed our figures (table VI). This explanation is not applicable for the most surprising result of our analysis, the early appearance of elevated pressures in the women between 30 and 39, neither is it applicable for the great difference in the age between 40 and 49, where out of the men there were only 12 per cent with pressure above 150 mm versus 41 per

cent among the women. There exists no mortality from hypertension or its sequelae among men of this age such as to produce this sex difference among the surviving.

It is a matter of importance to correlate with the findings of this study the results obtained from autopsies. We are fortunate to be able to compare with our blood pressure studies the detailed report by Bell and Clawson,²⁷ based upon a large autopsy material from the same community as our patients. Bell and Clawson used hypertrophy of the heart (in the absence of valvular lesions or chronic glomerulonephritis) as the chief diagnostic sign. (For details see original article.) Thus it is clear that only such elevated blood pressures as were sustained over a sufficiently long time and at a sufficiently high level to produce a marked hypertrophy of the heart, were included in the study of Bell and Clawson. In their total material of 4 578 autopsies on individuals between 21 and 80 years of age they found 420 cases of chronic hypertension. Among these they found the corrected ratio of men to women to be 1.4:1. For the whole hypertension group the causes of death are

given as follows myocardial failure, 45 per cent, cerebral accident, 19 per cent, coronary sclerosis, 16 per cent, renal failure, 9 per cent, miscellaneous, 11 per cent. In the group of coronary sclerosis the ratio of men to women was as 27 1. Eliminating the cases of coronary sclerosis, the ratio for the remainder becomes 11 1. In the study of Bell and Clawson about 15 per cent of the individuals who died at an age above 50 were afflicted with hypertension.

On the basis of the previous discussion it seems justifiable to state that elevated blood pressures are found both earlier in life and with greater frequency among women than among men. From the type of the curves and character of the tables presented there seems to be no support for any correlation of elevation of blood pressure in women with the phenomenon of menopause. It further seems obvious that there exists a rather large number of individuals with pressures temporarily or permanently in excess of average levels, who do not develop significant clinical or pathological sequelae from such pressures. There are probably a larger number of women than of men with such benign pressures at high levels.

Practically all discussions of normal systolic blood pressure in men have been carried on with the hope of being able to draw a definite line of distinction between normal pressure and an early pathological hypertension. The hope of being able to distinguish once and for all between a normal pressure and an early hypertension is a futile one. When cases of higher pressures start to accumulate in num-

ber as in the group of women between 40 and 49 for instance, they become significant in a different way, now they form to a great extent the lower pressures among a group of hypertensions as indicated in an indirect way by the enormous increase of the standard deviation of the mean for this group, and it is statistically impossible to determine the upper limit of a normal pressure for this age. We are at a loss, because there is no rule for a selection of our normal material, the needed dividing line being at the same time what we search for, and what we need to apply in order to find that for which we search. For practical purposes the way out of this dilemma is the one followed by the actuaries of the life insurance companies, the determination of the pressure above which the death rate rises above the rate known to hold for the same age groups without elevation of blood pressure. In this connection it is of interest that Fisher²⁸ found a normal mortality rate in 2,610 men from 40 to 60 years of age with an average systolic pressure of 142 mm. Fisher,²⁸ Rogers and Hunter,²⁹ and Frost³⁰ have shown an extra mortality in individuals with systolic pressure 10 to 15 mm above the insurance averages. They also show a marked progressive increase in extra mortality with each group showing further elevation of systolic pressure. Such averages, however, do not furnish a sharp dividing line between normal and abnormal blood pressure, but merely a line above which the pressure is more apt to be associated with significant organic changes.

CONCLUSIONS

1 The statistical analysis shows an increase in mean value of systolic and diastolic blood pressure with age, the most marked rise occurring a decade earlier for women than for men. The relative variation increases over the age period but has a tendency to rise abruptly and remain relatively constant between rises. These rises also occur one decade earlier for women than for men.

2 The absolute variation is greater for women than for men. There is a statistically significant difference in mean value for men and women after 30 to 40 years of age.

3 A statistically significant difference is also shown in incidence of blood pressure of higher groups for women in comparison with men. The

averages for men and women in the higher groups do not show a significant difference.

4 The clinical significance of blood pressure of equal degree must be considered independently in men and women. A given elevated blood pressure is more apt to be benign in nature and if of pathological consequence to run a longer course in women than in men. Hypertension as a cause of death is as frequent in men as in women even though the incidence of blood pressure at higher levels is significantly greater in women. In the older age groups this difference is partially explained by the shorter course of the condition in men.

(The author wishes to express to Miss Marie M. Ness his appreciation of her invaluable aid in the statistical analysis.)

REFERENCES

¹GOEPP. Cited by Symonds.⁵

²MACKENZIE, L. F. Blood pressure with a special reference to the diastolic, *Assoc Life Ins Med Dir Am, Abst Proc*, 1915-16, iv, 221-237.

³FISHER, J. W. Further report of the diagnostic value of blood pressure covering a period from August 1, 1907, to August 1, 1915, *Assoc Life Ins Med Dir Am, Abst Proc*, 1915-16, iv, 203-221.

⁴HUNTER, A. W. Blood pressure, what affects it?, *Proc. Assoc Life Ins Pres*, 1923, xvii, 64-81.

⁵SIMONDS, B. The blood pressure of healthy men and women, *Assoc Life Ins Med Dir Am, Abst Proc*, 1922, ix, 22-58.

⁶ADAMS, S. F. A study of the blood pressure of patients with diabetes mellitus, *Am Jr Med Sci*, 1929, cxxxvii, 195-201.

⁷JUDSON, C. F., and NICHOLSON, P. Blood pressure in normal children, *Am Jr Dis Child*, 1914, viii, 257-269.

⁸FABER, H. K., and JAMES, C. A. The

range and distribution of blood pressures in normal children, clinical application of statistical methods to the interpretation of deviation from the normal average, *Am Jr Dis Child*, 1921, xiii, 7-28.

⁹ALVAREZ, W. C. Blood pressure in university freshmen and office patients, *Arch Int Med*, 1920, xxxi, 381-404.

¹⁰ALVAREZ, W. C. Blood pressure in 15,000 university freshmen, *Arch Int Med*, 1923, xxxiii, 17-30.

¹¹DIFIL, H. S., and SUTHERLAND, K. H. Systolic blood pressure in young men including special study of those with hypertension, *Arch Int Med*, 1925, xxxv, 151-173.

¹²DIFIL, H. S. Personal communication.

¹³SALLER, K. Über die Altersveränderungen des Blutdruckes, *Ztschr f d ges exper Med*, 1928, lvi, 683-709.

¹⁴GRUMAN, J. Hypertensionstudien. Alters- und Berufsverschiedenheiten im arteriellen System, *Ztschr f kl Med*, 1927, cxi, 310-319.

- ¹⁵GAGER, L. T. The incidence and management of hypertension, Jr Am Med Assoc, 1928, xc, 82-86
- ¹⁶RISEMAN, J. E. F., and WEISS, S. The age and sex incidence of arterial hypertension, Am Heart Jr, 1929, v, 172-190
- ¹⁷WILDT, H. Über Blutdruck in Greisenalter, Zentralbl f Herz - u Gefasskr, 1912, iv, 41-49
- ¹⁸BOWES, L. M. Blood pressure in the aged, Jr Lab and Clin Med, 1917, ii, 256-257
- ¹⁹RICHTER, A. Über Blutdruck im höheren Lebensalter Zugleich ein Beitrag zur Klinik des Hochdrucks, Deutsch Arch f klin Med, 1925, cxlviii, 111-120.
- ²⁰DAVIS, H. J. Notes on blood pressure in old age, Human Biol, 1930, ii, 264-276
- ²¹O'HARE, J. P. Vascular reactions in vascular hypertension, Am Jr Med Sci, 1921, clxx, 269-380
- ²²MOSENTHAL, H. O., and SHORT, J. J. The spontaneous variability of blood pressure and the effects of diet upon high blood pressure, with special reference to sodium chloride, Am Jr Med Sci, 1923, clxxv, 531-550
- ²³KYLIN, E. W. V. Die Hypertoniekrankheiten, 1926, J Springer, Berlin
- ²⁴AYMAN, D. Normal blood pressure in essential hypertension, Jr Am Med. Assoc, 1930, xciv, 1214-1218.
- ²⁵BLACKFORD, J. M., BOWERS, J. M., and BAKER, J. W. Follow-up study of hypertension in women, Jr Am Med Assoc, 1930, xciv, 328-333
- ²⁶RIESMAN, D. Hypertension in women, Jr Am Med Assoc, 1919, lxxiii, 330-333
- ²⁷BELL, E. T., and CLAWSON, B. J. Primary (essential) hypertension, study of 420 cases, Arch Path, 1928, v, 939-1002
- ²⁸FISHER, J. W. Risks rejected for high blood pressure only, Assoc Life Ins Med Dir Am, Abst Proc, 1922, ix, 63.
- ²⁹ROGERS, O. H., and HUNTER, A. W. Mortality study of impaired lives, Assoc Life Ins Med Dir Am Abst. Proc, 1923-24, x, 43-60
- ³⁰FROST, H. M. Hypertension and longevity, Bost Med and Surg Jr, 1925, cxciii, 241-251

The Action of Benzol, Roentgen-Rays and Radium On the Blood and Blood-Forming Organs

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THIS paper is based on a review of over 1200 articles. This review, made in collaboration with Dr Laurence Selling, is to be published in "The Handbook of Morphological Hematology", P B Hoeber, Inc, and may be consulted for bibliography and detailed observations. Only the more clinically significant inductions with some suggestions for therapy derived from these inductions will be presented here.

It is well known that benzene, ar-sphenamines, radio-active substances, and roentgen-rays will, under certain conditions, produce the clinical picture of aplastic anemia. The other hematologic syndromes which may be produced are less well known. These syndromes include agranulocytosis, thrombopenic purpura, erythrophthisis, or any combination of these, and even anemia of regenerative type, leucocytosis, thrombocytosis, or polycythemia occasionally occur.

Under the term "benzol" are included a variety of mixtures of benzene (C_6H_6) and related compounds, but the chief action has been definitely

shown to be due to benzene, itself. The description of the action of the pure substance, therefore, applies to mixtures containing it as well. It is a volatile liquid with a boiling point of $80.3^\circ C$ and is used extensively in industry as a solvent, particularly for rubber. It is absorbed from the skin, the subcutaneous tissues, the gastrointestinal tract, and the lungs.

The effects produced vary with the dosage and individual susceptibility. Large doses produce acute poisoning with symptoms of cerebral irritation, followed by convulsions, coma, and death, or recovery within a few hours. Visceral hemorrhages occur but no marked hematologic changes have been reported. A somewhat smaller continued dose results in the development of the clinical and hematologic picture of agranulocytosis, purpura hemorrhagica, or both, after an interval of two or more days and death usually within twenty days, but the bone marrow shows complete or almost complete aplasia, although anemia is slight or absent. As the dosage is further decreased, the interval to the development of symptoms increases and the picture resulting may be that of erythrophthisis, agranulocytosis, or purpura hemorrhagica alone or in any

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combination, the marrow picture corresponding to that one would expect from the blood findings. Very small doses result in evidence of increased cell formation, such as the appearance of immature neutrophils and reticulocytes in the blood, leucocytosis, thrombocytosis and polycythemia, together with marrow hyperplasia. Even the development of leukemia or pernicious anemia has been reported but is not well substantiated.

The factors responsible for the great individual variations in susceptibility are largely unknown, but, in general, women are more susceptible than men and men more susceptible than the lower animals. Aplastic pictures are reported more commonly in man and agranulocytic pictures in animals, but this would seem to depend in part, if not largely, on the dosage. Hematologic changes may progress or develop as long as a month after exposure has ceased. The action is chiefly on the bone marrow and to a less extent on the lymphatic tissues. Opinions differ as to whether direct damage occurs to the cells in the circulating blood, if such damage does occur, it is certainly slight.

Industrial poisoning is not uncommon. Serious poisoning can be prevented by periodic hematologic studies, elimination of the more susceptible individuals, and reduction of exposure to a minimum by local ventilation and use of less toxic substitutes. The use of benzene in the treatment of leucemia is successful in producing reduction in the white blood cells and in the platelet count, but its use is not recommended because of the danger of producing aplastic anemia

or too great a fall in the white cell count, and because of the superiority in the clinical results obtained from the use of roentgen-rays and radioactive substances.

Drugs of the arsphenamine group, which contain the benzene ring, are known to have produced all of the above described findings; but the results in a given case apparently depend almost entirely on individual susceptibility rather than on the size and number of the doses. Hematologic changes resulting from therapeutic dosage are rare, difficult to anticipate, but likely to be serious.

The external application of radioactive substances and roentgen-rays will be discussed together, since the effects are produced almost entirely by the action of gamma rays. The tissue involved depends on the penetrative power, distance, filtration, and area exposed, and the effect on this tissue depends on the quantity of energy absorbed by it. When the penetration is sufficient to reach the bone marrow and the entire body is exposed, all the effects described for benzene may be produced, but lymphatic tissues and tissues unrelated to the hematopoietic system are much more severely damaged than by benzene, while complete aplasia of the marrow is more difficult to produce. The circulating lymphocytes show a correspondingly greater alteration. Local application of gamma rays gives a similar pathologic picture in the area exposed, but the compensatory response in the unexposed tissue alters the hematologic picture. For some unexplained reason, exposing the spleen alone may hasten coagulation, decrease the total white cell count, or

increase the platelets. True aplastic anemia rarely, if ever, results from therapeutic or occupational exposure to roentgen-rays if even minimum modern precautions are observed, but radio-active substances are somewhat more dangerous because of the greater penetration of the rays.

Gamma rays have been used in the treatment of almost all diseases of the blood and blood-forming organs. Such treatment gives very striking reduction of lymphatic tumors, such as enlarged thymus, Hodgkin's disease, lymphosarcoma and lymphatic leukemia. Lymphatic enlargements due to infection may also be decreased in size. It is debatable whether the length of life has been increased in Hodgkin's disease, lymphosarcoma and chronic leukemia, but it seems certain that the length of useful and comfortable life has been prolonged. Gamma rays seem valueless or contraindicated in acute leukemias. The clinical improvement in leukemias bears no direct relation to the fall in white blood cells. In myelogenous leukemia, opinion is divided as to whether therapy should be directed chiefly to the spleen or to the bone marrow. All are agreed that therapy should be stopped soon enough to avoid the development of a leucopenia. Gamma ray therapy is one of the most effective methods of reducing the red cell count and producing symptomatic relief in polycythemia. Small doses of gamma rays to the marrow have been reported to give favorable results in agranulocytosis but certainly an agent which is known to be capable of producing this syndrome should be used with caution. Gamma ray therapy to the spleen

sometimes causes cessation of gynecologic bleeding or the hemorrhages of purpura hemorrhagica but is not the method of choice.

The effects of radio-active substances internally depend almost entirely on the alpha rays. They are most marked on the bones and marrow because these substances show elective localization in the bones and the alpha rays have extremely slight penetrative power but tremendous destructive energy. The duration of action depends on the rate of disintegration of the particular radio-active substance. All forms with half-disintegration periods of more than a few days are extremely dangerous and should not be used internally. The dosage producing symptoms is extremely minute, a few micrograms having caused death and the interval between exposure and the onset of symptoms may be several years. Any of the syndromes described for benzene may result, but aplastic anemia is by far the commonest. It is usually associated with necrosis of bone and osteogenic sarcoma is a late sequel. Several cases of fatal poisoning have been reported among workers who have ingested luminous paint or have inhaled emanation or radio-active dust in the manufacture, handling or therapeutic use of radio-active substances. Alpha ray therapy has been tried in most of the diseases of the blood and blood-forming organs, but as it is much more dangerous and so much less effective it has been discarded in favor of gamma ray therapy.

A few general conclusions seem justified from the foregoing. Toxic effects from the dose of

must be excluded in the differential diagnosis in patients presenting the syndromes of agranulocytosis, thrombopenic purpura, erythrophthisis, or aplastic anemia. The fact that this group of syndromes or various combinations of them may be produced by any one of these agents suggests that they are closely related conditions and that the so-called idiopathic forms may also be related and due to the actions of toxins, possibly non-bacterial, on the marrow. The fact that resistance to infection is greatly decreased in all of these syndromes in which mature neutrophils are scarce in the blood stream suggests that the severe infections of mucous membranes characteristic of idiopathic agranulocytic angina, aplastic anemia, and acute leukemias may also be due to the scarcity of mature neutrophils in the blood, in other words, that the infection is secondary to the granulopenia and is not the etiologic factor of the disease.

Experimental work on the therapy of agranulocytosis, thrombopenia, and erythrophthisis could be done on animals in which these syndromes have

been produced by one of these agents, preferably benzene. On the basis of the evidence at hand, it would seem that the direction of therapy should be to supply an adequate number of white cells, red cells and platelets to the circulating blood until the marrow can be restored to activity. Repeated transfusions can easily maintain a normal red cell count, but if a sufficient number of transfusions is given to compensate for the more rapid destruction of white cells and platelets, a polycythemia results. This difficulty may be overcome by concentrating the white cells and platelets from a large quantity of blood. The action of pentose nucleotide and small doses of roentgen-rays on depressed marrow should be investigated further. The only hope for a real cure of leukemias would seem to lie in complete eradication of abnormal cells. Benzene or some related compound may have a sufficient specificity to accomplish this, if the patient can be kept alive during the period of complete aplasia. Investigation of these theories is in progress.

A Further Study of a White Family Showing Elliptical Erythrocytes

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ALTHOUGH it is not uncommon to encounter occasional oval, elliptical or even rod-like erythrocytes in blood smears from perfectly healthy persons, a predominance of such forms in the absence of severe anemia is exceptional.

Two interesting and curious morphological abnormalities involving the erythrocytes may occur in healthy individuals, first, so-called sickle cell anemia which has never been found except in persons of negro extraction and second, a condition characterized by the predominance of elliptical or oval red blood cells and occurring in both whites and negroes. Of the two, sickle cell anemia is by far the more common, the incidence being variously estimated at from 0.6 per cent (Mulherin and Houseal¹) to 7.2 per cent (Cooley and Lee²). Huck and Bigelow³ were the first to demonstrate that sickle cell and elliptical cell deformities are entirely different conditions with hereditary transmission as the sole common feature.

Dresbach⁴ who was the first to recognize and record an instance of ellip-

tical erythrocytes in a human being suspected the congenital nature of the anomaly but was unable to prove the point since the one available relative of the patient had normal blood. The first suggestive evidence was furnished by Bishop,⁵ and Huck and Bigelow³ but full confirmation was lacking until the appearance of the study of Hunter and Adams,⁶ 1929, of van den Bergh⁷ 1931, and of Cheney⁸ in 1932.

In 1929 the author with the collaboration of Dr R. B. Adams reported the results of an investigation of the blood from sixteen persons of pure Dutch extraction. Of these twelve showed elliptical erythrocytes and were distributed as follows: a father, each of his eight children (five daughters and three sons) and three of his six grandchildren. In the third generation two girls and one boy were affected, these being the offspring of two daughters both of whom exhibited the abnormality. In contrast to previous reports by others several members of this family were more or less anemic and one had a well marked anemia of the secondary type with no obvious cause.⁶

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*Adrian S. The blood of the patient examined was 13.22 gms. per 100 c.c. of plasma, 4.56 million red cells per c.c., hemoglobin 10.12 gms. per 100 c.c. of plasma.

After the publication of our work a communication was received from Professor A. A. Hymans van den Bergh of the University of Utrecht inquiring if any members of this family still lived in Holland. Upon learning the family name, Professor van den Bergh assigned a member of his staff, Doctor Rehorst, to locate those descendants residing in Holland and to examine their blood. The highly illuminating results of this investigation were presented before the Dutch Royal Academy of Sciences in 1931.⁷ The study of the Holland branch of the group was made difficult by reason of their dispersion throughout the country and further by the refusal of certain parents to allow the blood to be taken from their children. Nevertheless four additional examples of elliptical erythrocytes were encountered. Inquiry disclosed that the father of the man who emigrated to the United States, who was the grandfather of the girl in whom the anomaly was first discovered by us, had been married four times. There were no living descendants of the first marriage. None of the children from the second and fourth marriages nor the grandchildren and great-grandchildren issuing from either of these marriages had oval red blood cells. It thus appeared probable that the man living in America, who was one of several children from the third marriage, had not acquired the ab-

normality from his father but through his mother, the third wife.

Accordingly van den Bergh instituted a search for other children issuing from the third marriage and for relatives of the third wife who was not living at the time of the investigation. Upon inquiry it was learned that she was one of seven children, all of whom were dead. However, five of the eight children of a sister of the third wife of J. K1 were discovered and examined. Three members of this branch who had ovalocytes refused to allow blood to be taken from their children so that only the offspring of one son with, and of a daughter without ellipses, could be studied. The son had transmitted the anomaly to one of his two daughters. Of further interest was the absence of elliptical corpuscles in all of the three sisters of the man living in the United States in whom we had previously found such cells.

The present report is largely supplementary to the first⁶ and had its inception with the opportunity to study from the time of birth the blood of a baby daughter of Adriana S., in whom the condition was originally discovered. Also after the publication of the first paper⁶ I learned that a full brother of A. K1 living in Colorado had four children and that the wife of one of his sons was about to be confined. It appeared desirable, therefore, to continue the work and insofar as possible determine the incidence of elliptical erythrocytes in the entire family group.

Baby S., female, was born Dec. 22, 1931, at full term and proved to be normal and healthy in every respect.

⁷ The first 20 erythrocytes numbered 381 and 382 were from the present study. The rest of the 30 erythrocytes that were examined were from the blood of the man who was the father of the girl in whom the anomaly was first discovered by us.

Blood obtained from the umbilical cord at the time of birth was observed both in sealed wet preparations and in dried smears stained in the usual manner. In the sealed specimens a fair percentage of erythrocytes were oval and a few had a rodlike form. The exact number of each was not determined. The dried film contained a small number of oval cells but almost no greatly elongated or typical ellipses (figure 1). Three subsequent examinations of blood obtained by skin puncture on the day of birth and again on the fourth and twelfth days of life gave practically the same results. As is normal for a newborn child the number of erythrocytes and their hemoglobin content was high, 616

millions with 146 per cent hemoglobin (Sahli Osgood-Haskins' standard), 62 millions with 138 per cent hemoglobin, and 60 millions and 127 per cent hemoglobin, on the days mentioned above.

As a control the blood from six other babies of the same age was examined over the same interval of time. In two instances both the cord blood and that obtained after birth were found to contain occasional oval erythrocytes but the number was insignificant. After leaving the hospital the parents of the baby moved to another city thus making periodic examinations impossible. However, at the age of three months it was possible to obtain one further specimen of blood

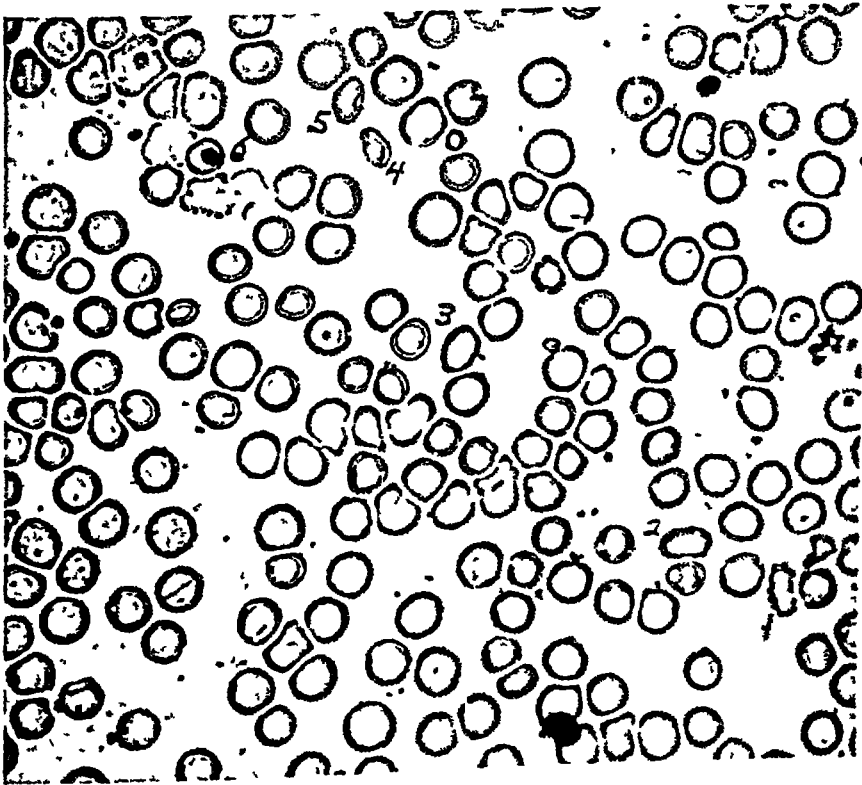


FIG 1 Baby S. Microphotograph of blood obtained from umbilical cord. 1 to 5 are oval erythrocytes, 6 is a normoblast.

which showed in fresh sealed preparations 44.4 per cent oval, 1.6 per cent elongated or irregular poikilocytes, and 54 per cent discoid cells. The percentage of abnormal forms in stained smears was not counted but comparison with the smears obtained during the first two weeks of life disclosed a very obvious increase (Figure 2). Many of the erythrocytes were now oval and in stained smears a fair proportion were rodlike with quite bluntly rounded ends. The number of erythrocytes and the hemoglobin could not be determined at this time.*

The placenta was placed immediately in ten per cent formalin and paraffin sections stained with hematoxylin and eosin were prepared. In the sections only a small percentage of oval

*I am informed that the baby died suddenly on April 30, 1932, while in apparent good health. A postmortem examination was not made.

erythrocytes could be seen in the maternal blood sinusoids, even where the cells were so widely separated that pressure artefact and tangential position could be eliminated. This finding is especially interesting in view of the very high percentage of abnormal erythrocytes in the circulating blood of the mother. The small size of the channels through the chorionic villi made it very difficult to find any erythrocytes which were not molded by pressure and nothing can be said as to the presence or absence of abnormal forms in the fetal side of the placental circulation. The same is true for the blood in the cord vessels. The placentas from ten other women fixed and stained in the same way served as controls. Oval erythrocytes occurred in two instances although the number was distinctly less than in the placenta from Mrs. S.

A study of the blood of the Colorado divi-

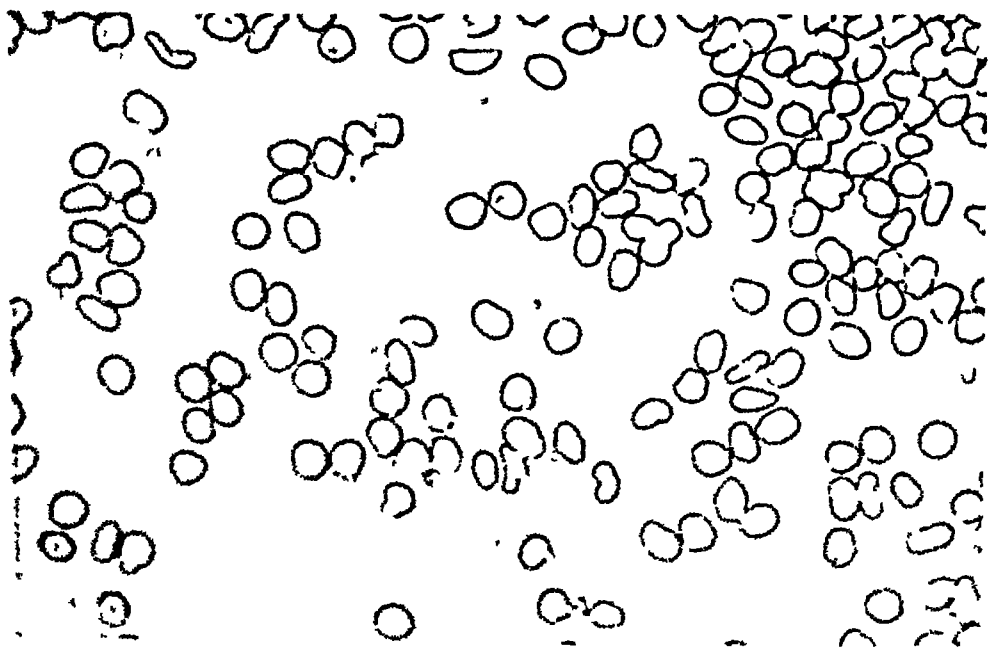


FIGURE 2. Blood smear from the mother of the child who died on April 30, 1932. The smear shows a high percentage of abnormal forms, including many oval cells.

sion of the family was made possible by the hearty cooperation of Dr James S Orr of Fruta, to whom the writer wishes to express his gratitude and appreciation for obtaining samples from the members of the family residing there

The Colorado group consists of Mr G Kl (full brother of A Kl of Montana), who has four children and two grandchildren, (Chart 1)

The blood of G Kl contains comparatively few oval red blood cells in sealed fresh specimens, the number computed on the basis of a count of one thousand erythrocytes being 82 per cent Still fewer occur in stained

films The total number of corpuscles and percentage of hemoglobin were not determined but Dr Orr informs me that the man is in good health

John, son of G Kl, is a healthy male 28 years of age Fresh blood could not be obtained but in dried smears a small percentage of erythrocytes are oval in outline The red cells number 5,400,000, and the hemoglobin is 85 per cent (Tallquist)

Of the three remaining children a daughter, Neisje, has 108 per cent oval and 08 per cent irregularly formed poikilocytes in wet films and

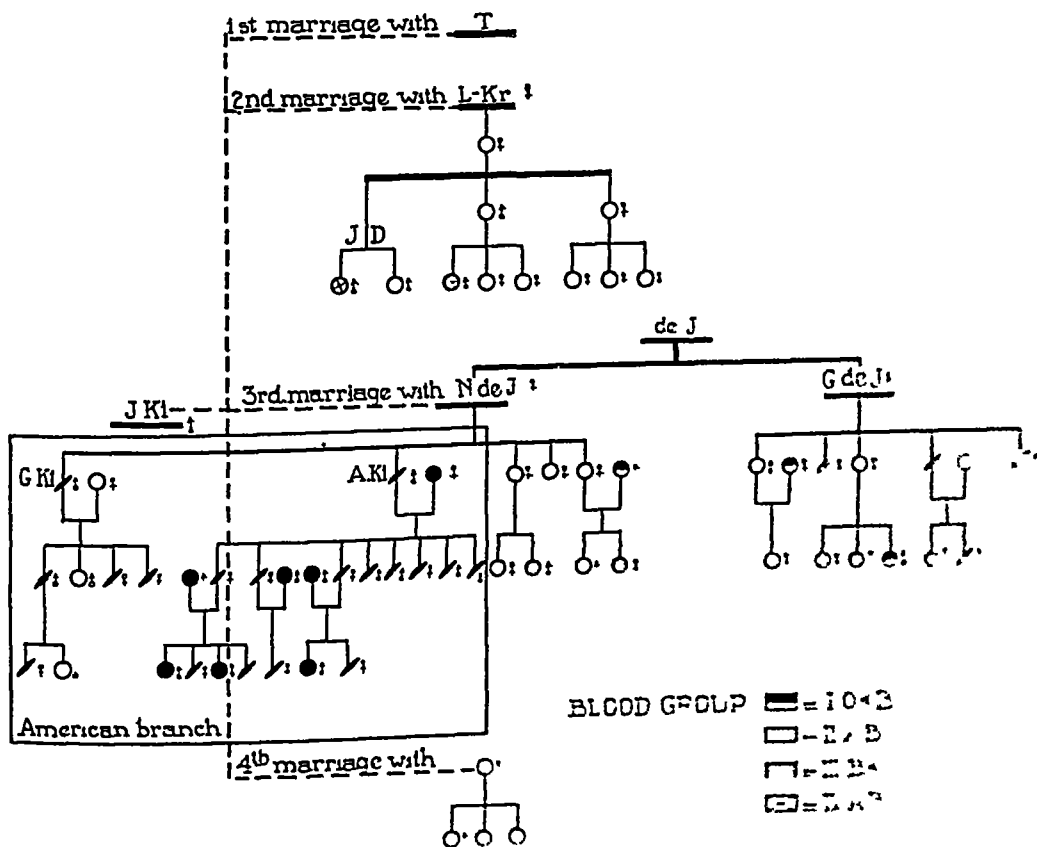


CHART I Occurrence of elliptical erythrocytes in three generations of the Colorado group. The American branch of the group has been set off by the rectangular figure in the diagram. The remaining members of the family, all of whom were studied by van den Bergh. The chart shows the distribution of the blood group and indicates that it entered the family through the third generation. Individuals are designated by ellipses.

approximately the same number in dry smears. A sister, Mary, shows slightly fewer abnormal forms, 7 per cent oval and 0.6 per cent irregular erythrocytes. The fourth child (Ira) age unknown, has normal cells.

John K1. is the father of two children, a boy four years of age who does not exhibit the abnormality and an infant daughter whose blood on the seventh day post-partum contained in dry smears a few distinctly oval erythrocytes.

After completing the study of these persons I noted in a very recent paper by Terry et al.⁹ a statement to the effect that in their hands pressure upon the cover slip over a drop of blood often resulted in a great reduction and sometimes an almost complete disappearance of oval forms, with replacement by circular cells. In my preparations pressure had been applied in each instance. This may readily account for the low percentages of oval forms present in the wet suspensions. Unfortunately no further specimens of blood could be obtained.

SUMMARY

The combined genealogical charts of Hunter and Adams⁷ and of van den Bergh, together with further corroborative evidence submitted herewith, indicate that in the K1 family the condition of elliptical erythrocytes is inherited as a dominant trait, thus forming a striking example of inheritance of a peculiarity of a cellular component of the blood. Additional proof of the hereditary nature of elliptical erythrocytes is the occurrence in fourteen subjects of three generations

of the Italian-American family studied by Cheney.⁸

With one exception, that reported by Bernhardt,¹⁰ the abnormality has never been known to skip a generation but has appeared only in the offspring of affected persons and is transmitted with equal frequency by both sexes.

That the trait is truly a hereditary one is further shown by the presence of oval and rodlike erythrocytes in the blood of two newborn babies studied by the writer. In each instance one parent was similarly affected. In one of the babies from whom it was possible to secure several specimens, the number of abnormally formed red blood cells increased quite perceptibly between the age of twelve days and three months. According to Terry⁹ the adaptation of cells and serum to each other is still in progress at birth and continues for some time before permanent relations are attained and the blood group becomes established. Only on some such basis can one explain the striking increase of elliptic cells observed in Baby S. (figure 1).

Sections of the placenta from this case failed to disclose more than a few oval erythrocytes although the circulating blood of the mother contains a higher percentage of such cells than any other member of the family. Fixation in formalin may in part be responsible for the change in form. The occurrence of similarly shaped corpuscles in two of ten placentas from normal cases makes observations of this kind of doubtful value. Furthermore, in tissue sections it is very difficult to be certain that pressure from other cells has not altered the form of

erythrocytes In the writer's experience it is not uncommon to see numerous oval red cells in sections of many tissues and organs and little importance is attached to finding them in the case at hand

In a previous communication it was stated that the rôle of the erythrocytic anomaly as a cause of the anemia existing in several members of the K1 family was problematical The present study has thrown no new light upon this aspect of the condition and we are in agreement with Osgood and Haskins¹¹ that the red cell form is probably exaggerated by anemia but does not predispose to it

Including the five new instances of

hereditary elliptical erythrocytes reported herein, 57 examples of this condition are now on record It is probable that the anomaly is less rare than formerly supposed and that with more careful examinations of the blood it will be found with increasing frequency

The present report is supplementary to those of Hunter and Adams⁶ and of van den Bergh⁷ and its chief purpose is to complete the study of one large family group Certain interesting and important experiments of Terr⁹ et al⁹ concerning the nature and behavior of elliptical erythrocytes have been omitted largely because of inability to obtain sufficient blood

REFERENCES

- ¹MULHERIN, W A, and HOUSEAL, R W Sickie cell anemia from a pediatric point of view, *Tr Sect Dis Child, Am Med Assoc*, 1924, 77-88
- ²COOLEY, T B, and LEE, P The sickle cell phenomenon, *Am Jr Dis Child*, 1926, xxxii, 334-340
- ³HUCK, J G, and BIGALOW, R M Poikilocytes in otherwise normal blood (elliptical human erythrocytes), *Bull Johns Hopkins Hosp*, 1923, xxxiv, 390-393
- ⁴DRESBACH, M Elliptical human red corpuscles, *Sci*, 1904, xix, 469-470
- ⁵BISHOP, F W Elliptical human erythrocytes, *Arch Int Med*, 1914, iv, 388-392
- ⁶HUNTER, W C, and ADAMS, R B Hematologic study of three generations of a white family showing elliptical erythrocytes, *Ann Int Med*, 1929, ii, 1162-1174
- ⁷VAN DEN BERGH, A A HANNA On elliptic red blood-corpuscles (ovalocytosis), *K Akad van Wetens te Amsterdam*, 1931, xxxv, 749-754 (in Dutch)
- ⁸CHENEY, G Elliptic human erythrocytes, *Jr Am Med Assoc*, 1932, xcvi, 878-881
- ⁹TERR, M C, HOLLINGSWORTH, F W and EUGENIO, V Elliptical human erythrocytes, report of two cases, *Arch Path*, 1932, xiii, 193-206
- ¹⁰BERNHARDT, H Ovalocytose der Erythrozyten als Anomalie *Deutsch med Wchnschr*, 1928, lv, 987-989
- ¹¹OSGOOD, E L, and HASKINS, H D Laboratory diagnosis 1931 P B. Lippincott Son and Company, Philadelphia 215

Potassium Sulphocyanate: A Note on Its Use for the Painful Crises in Sickle Cell Anemia

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SICKLE cell anemia is a disease of unknown etiology, its prognosis is uncertain and its treatment is entirely symptomatic. In its active stage it is noteworthy for its spontaneous remissions and relapses. Most observers have found that treatments thus far suggested do not materially alter the course of the disease. No therapeutic procedure seems to influence the degree of sickling *in vivo*. Blood transfusions bring about remissions with uncertain regularity, and are of temporary value when so induced. They do on occasions tide a severely anemic patient over a critical period.

Liver diet has been tried by Sydenstricker and others without any favorable effect. Levy² reported on the use of liver extract in three patients over a period of a year. This treatment apparently accounted for an increase in the number of red cells as well as the hemoglobin percentage. With the improvement of the blood picture there came a definite improvement in symptoms and a tendency to

inhibition of sickle cell formation. In one of these patients it is reported that the sickle cells disappeared from the blood and in another the number of such cells was reduced. Levy's report constitutes the only evidence in the literature of a favorable influence on sickle cell formation by treatment. Yater and Mollari³ reported a case in which liver extract was given for two weeks with no especial influence on the hemoglobin and erythrocyte pictures. The reticulocyte count rose from 28 per cent to 90 per cent, but fell to 0.6 per cent a few days later. One of us has noted the temporary influence of blood transfusions on the anemic state of a sickle cell patient, and at the same time some symptomatic improvement; but has not observed any effect from the use of a liver dietary or liver preparation in other patients.

Many of the hemolytic features of familial hemolytic jaundice resemble those of sickle cell anemia. It was not surprising, therefore, when Hahn and Guller⁴ reported in 1927 that they had done a splenectomy on a child four years old with sickle cell anemia. In 1928 Black⁵ reported another splenectomy for the same disease, and at the

same time noted spectacular improvement in the patient operated upon in the previous year. Improvement in the second patient lasted for five months after operation. Stewart's⁶ patient showed no improvement while those of Bell, Kotte, Mitchell, Cooley and Lee⁷ improved only temporarily. Landon and Lyman⁸ reported the seventh splenectomy including that of Giddings cited by Bell et al. This was done in a child four years old and showed improvement nine months after the operation. The improvement observed was shown in the child's general condition, a lessening of abdominal pains with an increase in the hemoglobin percentage and red cell count. Fourteen months after splenectomy this patient still presented an anemia and the sickle cell trait. In a patient observed by one of us there was no amelioration of generalized bodily and abdominal pains after a splenectomy. There was observed however, an elevation in the hemoglobin and number of red cells, but the patient died after the lapse of a year of an unknown cause. No post-mortem examination was performed on this patient. It seems fair to state, then, that splenectomy has been disappointing as a therapeutic practice in sickle cell anemia in marked contrast to the results following this same operation on patients suffering with hemolytic jaundice. Splenectomy however, is followed by some temporary improvement in the blood findings and symptoms generally when the patient is the victim of sickle cell anemia.

There is a difference of opinion as to prognosis for the victims of this disease. Huck⁹ indicated that for those

with symptoms life rarely lasts longer than thirty years. Sydenstricker¹⁰ believed the prognosis to be good for adults but guarded for children. He found a high child mortality and much myocardial and renal disease in sickle cell families. His patients ranged in age from three months to sixty-seven years and all died of intercurrent disease—nephritic coma, meningeal hemorrhage, pyelonephritis, bronchopneumonia, and traumatic peritonitis. Josephs¹¹ found on the other hand that the mortality among sickle cell children and their families was not demonstrably higher than the average. He also noted that an infection was responsible for the transition in one patient from the latent to the active phase with a subsequent return to the latent condition. This is the only patient reported in the literature in whom latency developed when once an active phase had been established. Although death seems to be due generally to some intercurrent disease, Wollstein and Kreidel¹² reported two patients who seemed to have died of the disease *per se*. Franklin and Schwartz¹³ claimed that 50 per cent of patients with sickle cell anemia succumb to tuberculosis. Dolgopol and Stitt¹⁴ found that 52 per cent of 77 tuberculous patients revealed the sickle cell phenomenon. In addition, then to an unsatisfactory therapy we have in this disease a varied and uncertain prognosis. Anything which seems to offer the slightest hope of treatment would seem to be worthy of note and subsequent trial in other patients.

In accordance with this I wish to record our experience with

negro male patient 26 years of age. He was admitted to the Philadelphia General Hospital for the first time in October, 1926. His past history revealed that he had not been able to attend school regularly as a child because of frequent headaches, pain in the back and extremities. These aches and pains lasted two to three days and then would disappear for a month or more. They occurred more frequently in the winter than in the summer. On his first admission he complained of excruciating pain in the right leg and left arm. There was nothing especially noteworthy on physical examination except for marked tenderness over the right tibia and left arm. He had an evening rise of temperature to 102° F and a leucocyte count of 15,200. The differential count was normal. X-ray examination was reported as showing some slight osteosclerosis in excess of normal. A diagnosis of periostitis was made clinically; the periosteum was raised, and a small amount of sterile pus was evacuated. Pains continued in the left arm and right tibia in lesser degree after operation and at the end of three weeks he was quite well. No record was made of the hemoglobin or red cell estimations during this hospital stay.

After the original admission he was returned to the hospital on four other occasions because of complaining of severe pain in the extremities, back and joints. On the last two admissions he had severe aching and dull pain in the right leg and left arm. On the third admission he had severe aching and dull pain in the right leg and left arm. On the fourth admission he had severe aching and dull pain in the right leg and left arm. On the fifth admission he had severe aching and dull pain in the right leg and left arm. On the sixth admission he had severe aching and dull pain in the right leg and left arm. On the seventh admission he had severe aching and dull pain in the right leg and left arm. On the eighth admission he had severe aching and dull pain in the right leg and left arm. On the ninth admission he had severe aching and dull pain in the right leg and left arm. On the tenth admission he had severe aching and dull pain in the right leg and left arm. 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attacks. These pains were especially perplexing during his second hospital stay for it was not until his third admission that sickle cells were reported as being present in his blood. Throughout his period of residence in the hospital and during his attacks of periodic pain it was difficult to make this patient comfortable, even by the use of morphine sulphate in fair-sized doses given at frequent intervals. Although it was appreciated that he was experiencing the abdominal crises which occur in sickle cell anemia patients, surgical consultation was requested at least twice. After both consultations it was agreed that there was no indication for laparotomy in spite of the fact that he was jaundiced, vomited, and at times the pain and rigidity occurred over the gall bladder area.

The records of physical examination for all admissions describe the patient as a young adult negro appearing younger and smaller than normal for his age. He was well nourished and well developed muscularly. The pubic hair showed a feminine distribution and he had no axillary hair. His cervical, epitrochlear and inguinal glands were enlarged. The conjunctivae were jaundiced. The heart was enlarged to the left and a systolic murmur was present at both the aortic and mitral areas. The former murmur was transmitted to the vessels of the neck. The liver and spleen were not palpable. He presented dried stool balls which were excised during his fourth hospital stay. There were no uric acid concretions or uric acid bodies.

After a course of the ureteral catheter, the blood, the urine

no sugar, an occasional trace of albumin and a few leukocytes. Phenolsulphonephthalein elimination amounted to 55 per cent for the first hour and 15 per cent for the second hour. A glucose tolerance test yielded the following findings: Fasting blood sugar 82 mgm per 100 cc, thirty minutes after 100 gm glucose, 131 mgm per 100 cc, one and one-half hours after glucose, 95 mgm per 100 cc, three hours after glucose, 74 mgm per 100 cc. The one and two hour urines showed 0.4 per cent sugar.

Hemoglobin values varied considerably at different times, ranging from a low of 8.1 gm per 100 cc to a high of 10.9 gm per 100 cc. Numerous red cell counts were recorded from 2,240,000 to 3,750,000. The hemoglobin values and red cell counts varied within short periods of time. Leukocyte counts ranged from 10,900 to 19,400. The average differential count was: polymorphonuclears, 57, lymphocytes, 39, large mononuclears, 4, and eosinophiles, 1 per 100 cells. Reticulocytes never exceeded 5 per cent in number. Sick-shaped cells were present at all examinations, varying from 6 per cent to 50 per cent of the cells counted. Nucleated red blood cells were present at all times. As many as 44 were seen while counting 100 leukocytes in a stained preparation. Platelet counts are reported from 2,800,000 to 4,800,000. The clotting time was 3.5 minutes on an average of three determinations. The fragility test showed beginning hemolysis at 36 per cent salt solution at one time, and at 30 per cent at another. Hemolysis was complete at less than 20 per cent in both instances.

Blood chemistry determinations yielded the following results: sugar 80 mgm per 100 cc, blood urea nitrogen, 12 mgm, cholesterol, 165 mgm, phosphorus, 4.6 mgm, and calcium 10.4 mgm per 100 cc. The P_H was 7.44. The van den Bergh test showed a delayed reaction on three trials. The icterus index varied from 8 to 15.

Test meal studies always yielded some evidence for the presence of free hydrochloric acid. The highest amount found at any time amounted to 25 in terms of decimal normal sodium hydroxide solution. The highest total acid value was 60.

X-ray studies showed normal pulmonary fields, the heart enlarged to the left, and no unusual observations made in the aortic shadow. The gastro-intestinal investigations by x-ray were negative as was the cholecystographic study. The bones generally showed the characteristic changes of sickle cell anemia.

In our effort to control this patient's abdominal crises we resorted to many drugs and therapeutic endeavors. We did not, however, transfuse him because his blood was never severely anemic. The variation in hemoglobin content and red cell count did not seem to bear any relationship to his pain. Besides this, our own experience coupled with that of others did not seem to warrant a trial which would only be temporary. We did not advise splenectomy because his spleen was not palpable. If this operation is to be of any value it must appropriately be done in children in whom the organ is usually, but not always, larger than normal. These two factors were guided in this decision by the necessity

results which have followed splenectomy as reported in the literature

It is quite possible to accelerate or retard the sickling phenomenon *in vitro*. One such method consists in changing the PH of the suspension medium which contains the red cells. Hahn and Gillespie¹⁵ reported that the reduction of the blood PH from 7.3 to 7.25 causes immediate sickling. It is added, however, that while such an observation in application to the sickling phenomenon may be suggestive, it would seem to be of doubtful bearing on the genesis of circulating sickle cells. Nevertheless, with this lead we fed our patient for a period of time on a ketogenic diet and during another period added large doses of ammonium chloride. At still another time we prescribed massive doses of bicarbonate of soda. These practices had no apparent influence on the severity of attacks nor on their frequency. The same authors have shown that saturation of the blood with carbon dioxide will produce sickling and that the action can be reversed by saturation with oxygen. During an attack we placed the patient in an oxygen tent with no amelioration of symptoms. Indeed, nothing we did seemed to influence the amount of sickling as determined by counts done both on dried and wet preparations immediately after blood withdrawal. Hahn¹⁶ believes that there is a correlation between the severity of sickle cell anemia

and the number of sickle cells in the circulation. He has studied on the patient the effect of the administration of oxygen and the number of sickle cells in the circulation.

During the attack the number of

arations did not change the symptoms. There was some increase in the reticulocytes but no evident increase in the red cell count as the result of this therapy. Salicylates were exhibited in large doses with no appreciable effect on the pains.

During attacks we used nitroglycerin, atropine sulphate, and adrenalin chloride hypodermatically with no relief. These preparations were used with the thought that the pains might be vascular in origin or perhaps the result of some autonomic nervous system disturbance. There never was observed, however, any alteration in the blood pressure during attacks. The blood pressure averaged about 110 systolic, and 62 diastolic. During attacks we also gave some triple distilled water and calcium chloride intravenously without effect.

Examination of wet specimens of this patient's blood with dark field illumination (Dr S. W. Ludlum) showed an unusual degree of erythrocytic clumping. This phenomenon is closely related to that of rapid red cell sedimentation and probably results from relative dehydration, diminution of electrical charge and a lack of sodium and potassium salts. Graham and McCarty¹⁷ have found an increased sedimentation rate in sickle cell anemia. Dr Ludlum suggested the trial use of sodium and potassium salts together with potassium or sodium sulphocyanate in this patient, largely on theoretical grounds. Beginning on February 19, 1931, the patient received large daily doses of potassium citrate and sodium bicarbonate. He had previously received these two preparations with no effect.

able results, but now there was added one and one-quarter grains of potassium sulphocyanate given three times a day. On February 23, this dosage was increased to two and one-half grains three times a day and this medication was continued until March 6, 1931. During this time he was entirely free from pain and discomfort and was up and about the ward. He remained free from pain until March 11, 1931, when he again complained of pain in the shoulders and abdomen. Immediately on receiving the potassium sulphocyanate therapy there occurred again a prompt relief of symptoms. During the period of thiocyanate medication, no variations in the number of sickle cells were noted. He felt unusually well and on being denied the privilege of leaving the hospital in the regular way, he absconded April 16, 1931.

In view of the fact that no adequate explanation had been made for the pain symptoms occurring in sickle cell anemia, one of us has elsewhere ventured the opinion that they may be due to some transient alteration in the nervous system. This nervous alteration may be consequent upon the bone pathology which goes with this disease. Our patient presented extensive changes in his vertebrae and it may be that the pains are comparable to those occurring as the result of other vertebral diseases. On one occasion he seemed to obtain relief by the application of a tight torsal binder. No one has carefully studied at autopsy central, peripheral or autonomic nervous system material obtained from such patients. The pains are quite like the critical attacks observed with loco-

motor ataxia or perhaps the root pains occurring in various spinal diseases.

In this connection it is of interest to refer to the recent observations reported by Bancroft¹⁸ on the colloid chemistry of the nervous system. His studies together with others made in the Cornell laboratories tend to support Claude Bernard's theory as to the chemical mechanism production of anesthesia. This theory would attribute the anesthetic state to a coagulation of the nerve tissue colloids as brought about by all of the well known anesthetics. The thiocyanate radical has the property of peptizing these coagulated protein colloids so that following administration of a thiocyanate preparation after anesthesia, there occurs a more rapid return of the nerve tissue protein to its previous normal colloidal state than is true under the usual recovery condition following every day operative anesthetics. At least this is shown to be true for animals as reported in Bancroft's article. If transient anesthesia and paralysis occur as a result of some chemical change in nervous tissue a chemical mechanism may also be assumed for pain production. In any event it seems quite clear that sodium or potassium sulphocyanate might bring about a peptization of colloidal proteins under variable conditions. It is well known that the state of the body colloids is due largely to electrolytic ions. In the Hofmeister series the thiocyanate radical occupies the top position and is therefore the best disperser of electrical charges. Whether the matter would seem to rest on a highly theoretical point, there seems to be some justification for believing

that there is a rationale in using a thiocyanate salt with other salts of sodium and potassium under the circumstances which we assume to present themselves during the critical abdominal attacks as they occur in sickle cell anemia. This assumption is that the pains are due to changes brought about in the aggregation or dispersion of the body colloids in some way.

Naturally we can present no conclusions. We have herein set forth some therapeutic experiences with a patient having sickle cell anemia who

seemed to be promptly relieved of generalized bodily pains on two occasions after the exhibition of potassium thiocyanate, potassium citrate, and bicarbonate of sodium. In this disease, noteworthy for the spontaneous remissions and relapses which it undergoes, it is difficult to draw any conclusions as to the effects of therapy. We are therefore not prepared to say that our treatment was the effective agent. The results seemed to be significant, however. Further trial and observation are necessary before any conclusions may be reached.

REFERENCES

- ¹SEIDENSTICKER, V. P. Sickle cell anemia, *Med Clin No Am*, 1929, xii, 1451-1456.
- ²LIVY, J. Sicklemia, *ANN INT MED*, 1929, iii, 47-54.
- ³YATH, W. M., and MORTARI, M. Pathology of sickle cell anemia, report of a case with death during an "abdominal crisis", *Jr Am Med Assoc*, 1931, xcvi, 1671-1675.
- ⁴HARRIS, E. V., and GILLESPIE, I. B. Sickle cell anemia, splenectomy, *Arch Int Med*, 1927, xxxix, 233-254.
- ⁵HARRIS, E. V. Sickle cell anemia, *Med Clin No Am*, 1928, xi, 1171-1174.
- ⁶SEIDENSTICKER, W. B. Sickle cell anemia, report of a case with splenectomy, *Am Jr Dis Child*, 1927, xxv, 72-80.
- ⁷FRANKLIN, W., KOPPEL, R. H., MITCHELL, A. G., GILLESPIE, I. B., and LEE, P. Sickle cell anemia, Report of two cases in which splenectomy was performed, *Am Jr Dis Child*, 1927, xxv, 1923-1937.
- ⁸HARRIS, E. V., and GILLESPIE, I. B. Sickle cell anemia, *Arch Int Med*, 1927, xxxix, 233-254.
- ⁹HARRIS, E. V. Sickle cell (dropers) anemia, *Am Jr Med Sci*, 1928, clxxv, 209-217.
- ¹⁰GILLESPIE, I. B., and McCARTHY, S. H. Sickle cell anemia, *Jr Lab and Clin Med*, 1927, vi, 546-547.
- ¹¹POSSON, W. D., and PETERSON, E. L. Sickle cell anemia, report of a case, *Am Jr Dis Child*, 1927, xxv, 1923-1937.
- ¹²JOSEPHS, H. W. Clinical aspects of sickle cell anemia, *Bull Johns Hopkins Hosp*, 1928, xlii, 397-398.
- ¹³WOLSTEIN, M., and KRIBBLE, K. V. Sickle cell anemia, *Am Jr Dis Child*, 1928, xxxvi, 998-1011.
- ¹⁴FRANKLIN, W., and SCHWARTZ, I. S. Sickle cell anemia, *Jr Lab and Clin Med*, 1930, xi, 519-527.
- ¹⁵DORGOPOL, V. B., and STITT, R. H. Sickle cell phenomena in tuberculosis patients, *Am Rev Tuberc*, 1929, xix, 451-460. *Abst Jr Am Med Assoc*, 1929, xxi, 1795.
- ¹⁶HARRIS, E. V., and GILLESPIE, I. B. Sickle cell anemia, *Arch Int Med*, 1927, xxxix, 233-254.
- ¹⁷GILLESPIE, I. B., and McCARTHY, S. H. Sickle cell anemia, *Jr Lab and Clin Med*, 1927, vi, 546-547.
- ¹⁸POSSON, W. D., and PETERSON, E. L. Sickle cell anemia, report of a case, *Am Jr Dis Child*, 1927, xxv, 1923-1937.
- ¹⁹JOSEPHS, H. W. Clinical aspects of sickle cell anemia, *Bull Johns Hopkins Hosp*, 1928, xlii, 397-398.
- ²⁰WOLSTEIN, M., and KRIBBLE, K. V. Sickle cell anemia, *Am Jr Dis Child*, 1928, xxxvi, 998-1011.
- ²¹FRANKLIN, W., and SCHWARTZ, I. S. Sickle cell anemia, *Jr Lab and Clin Med*, 1930, xi, 519-527.
- ²²DORGOPOL, V. B., and STITT, R. H. Sickle cell phenomena in tuberculosis patients, *Am Rev Tuberc*, 1929, xix, 451-460. *Abst Jr Am Med Assoc*, 1929, xxi, 1795.

An Assay of Goldenrod as a Cause of Hay Fever

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GOLDENROD, apparently our most popular aspirant for the title of "national flower" has in years past been reputed to be the principal cause of autumnal hay fever and asthma. Our modern concept of the etiology of pollen asthma has demonstrated that wind borne pollens are of far greater importance in this malady than are the pollens of those plants which are cross fertilized by insects. Indeed, the importance of wind distribution has been so emphasized, that prominent students of allergy have stated that goldenrod and other insect pollinated plants are of very little importance in the causation of pollen allergy. The idea is now quite general that goldenrod, like the rose and daisy, is always purely a local problem. If goldenrod be brought into a house for decorative purposes a sensitive individual may have trouble. Outside of this, the heavy sticky pollen is carried on the wind only for short distances and may therefore be easily avoided.

The summer of 1931, in Virginia at least, was an unusual one for plant growth, particularly for weed growth and the following observations have convinced the writers that under certain conditions at least, goldenrod

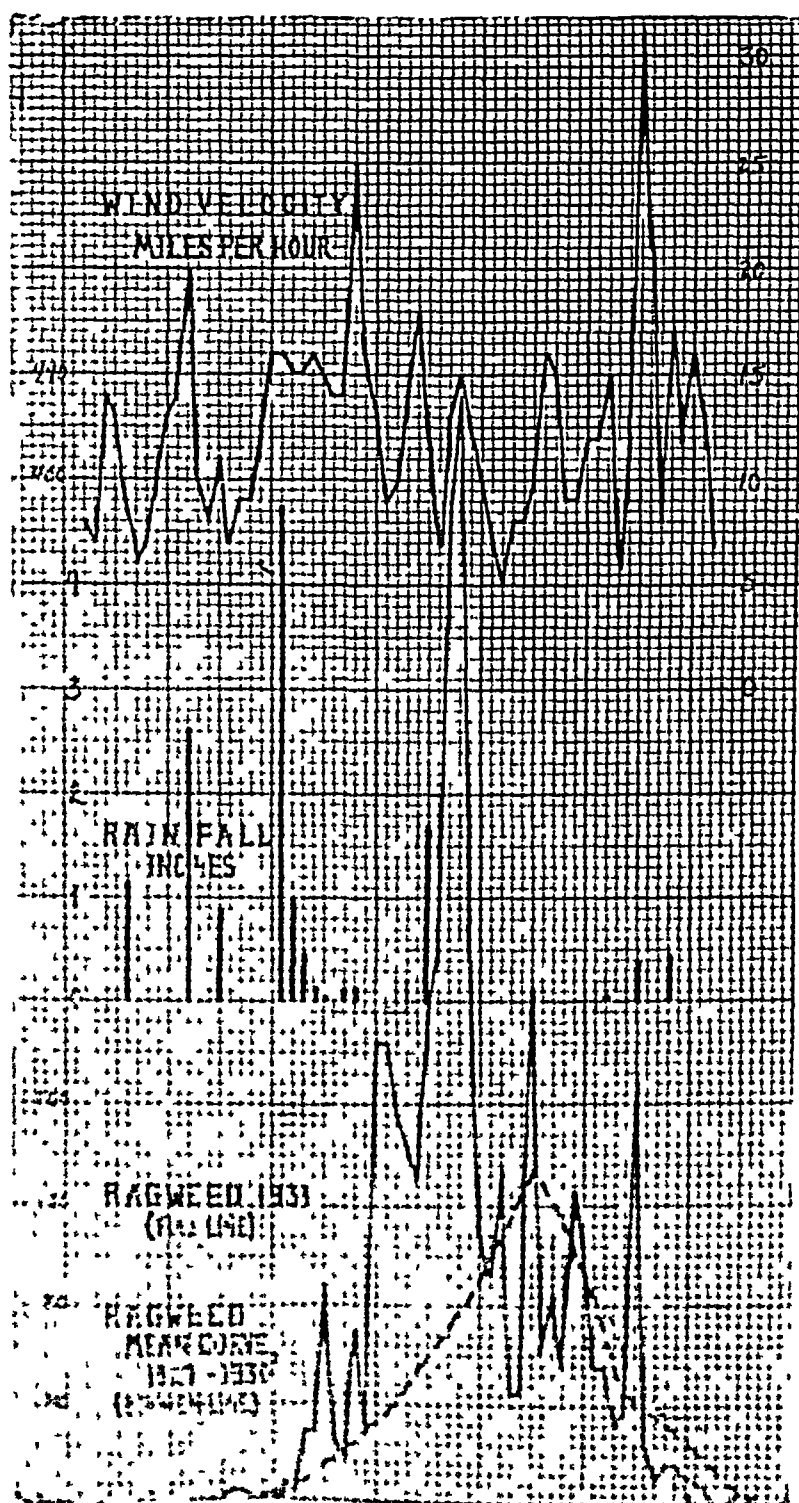
sensitization may be a factor requiring treatment.

HEAVY POLLIN PREVALENCES IN 1931

The ragweed curve for 1931 showed an unusually heavy pollen prevalence (chart I). We have kept daily curves of atmospheric ragweed pollen prevalence in Richmond since 1927. The average maximum prevalence for the four years, 1927 to 1930, was 116 grains per cubic yard of air. The highest prevalence prior to 1931 was 194 on September 22, 1928. The highest prevalence in 1931 was 138 on September 7. This is well over twice the highest daily prevalence in the preceding four years. Furthermore, the prevalence throughout the first half of the 1931 ragweed season was very much higher than in preceding years.

There were very definite meteorological reasons for this. In August, 1930 we had an unusual drought which delayed the onset of pollination for about ten days. On August 28, of that year there occurred a very heavy rainfall with 18 inches of rain in 24 hours. Within a few days pollen appeared in the places where it had been withheld. This was followed by a heavy prevalence so that the average for the preceding year

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This is the first factor in explaining the very heavy prevalence of the succeeding year, 1931 a heavy distribution of ragweed pollen in 1930, presumably with a consequent heavy distribution of fertilized seed

July, 1931, had a normal rainfall in Richmond with an average temperature (80°F), two degrees higher than the usual average for July With adequate rainfall and a high, but not too high, temperature, there were therefore good growth facilities in July In August the temperature was average but we had an extremely abundant rainfall (11.4 inches), more than had been recorded for any August since the Richmond Weather Bureau was established in 1871 Finally, early in the ragweed season there were several days of high wind velocity which naturally carried large amounts of pollen into the air (chart I)

These four factors, wide distribution of seed in 1930 good growth facilities in July, 1931, abundant rainfall in August and high winds early in September, were responsible for the tremendous pollen concentration in September in the vicinity of Richmond, as exemplified by the ragweed curve

Conditions in the country corresponded to conditions in the air Ragweed, both giant and dwarf, seemed to be nearly everywhere In the ditches along the roadsides wherever one might drive there was an unusual abundance of ragweed But the wide distribution of vegetation was not limited to this particular plant The other weed whose abundance was most striking was golden-

rod It was every bit as abundant as the ragweed and as one would drive along the country roads entire fields would appear a golden yellow from masses of goldenrod Conditions favoring growth had also produced unusually large individual plants It was not at all unusual to see stalks of goldenrod over six feet high (figure 1) It became obvious that an indi-



FIG. 1 Goldenrod plants over six feet tall

vidual sensitive to goldenrod could move into the country without being exposed to heavy concentrations of this pollen

But the observation which caused us to wonder whether pollen from too distant a source could carry pollen could not carry pollen from the cover of pollen grains from the pollen of goldenrod could be carried by our pollen traps The pollen traps

the eighth floor of an office building in the center of a city of nearly 200,000 population. It is at once obvious that this unusual pollen must have been carried to appreciable distances and that individuals even in the center of town were being exposed to it.

Goldenrod pollen is easily distinguishable from that of ragweed, but since there are many varieties of goldenrod and since the pollen grains differ in appearance in some of these varieties, some of the pollen was obtained directly from the goldenrod in the field for comparison with that found on the plates (figure 2). While the pollens appear to be the same, one cannot state absolutely, from morphologic resemblances, that the pollen on the plate is actually that of goldenrod. However, this appeared to be the case. In any event, an unusual pollen was being deposited on the plate. This indicated that hay fever sufferers were necessarily being exposed to this unusual pollen. The pollen appeared to

be that of goldenrod. Goldenrod was unusually profuse around the city and to a certain extent in the city.

THERAPEUTIC STUDIES

Allergists have known that it is not uncommon for an individual to react positively, on testing, to goldenrod extract. However, this has been overshadowed by the observations that goldenrod is insect pollinated, that the same individual is usually ragweed sensitive, and that ragweed desensitization alone usually relieves these persons of their symptoms. Therefore, in spite of positive reactions it has been customary not to desensitize with goldenrod.

In our experience, for every 100 persons sensitive to ragweed, 30 are found sensitive to goldenrod. In the majority of instances the goldenrod sensitive individual is also sensitive to ragweed.

Granting the frequency of goldenrod sensitivity, it becomes obvious that if such a person is exposed to golden-



rod pollen he may manifest symptoms and that if goldenrod pollen may be carried farther than we had supposed, this sensitivity may be an important one in the production of symptoms. With this idea in mind, as soon as the goldenrod-like pollen appeared on the plate, we investigated the records of those ragweed sensitive individuals who, following perennial or pre-seasonal treatment, had not obtained what they considered adequate relief. During the season there were 23 ragweed sensitive patients under treatment who had also been tested with goldenrod. Thirteen were negative to goldenrod and ten had reacted positively to it. Of the thirteen not sensitive to goldenrod, nine had received 90 per cent relief or better. However, of the ten who were sensitive to goldenrod seven had received 90 per cent relief or better, without goldenrod desensitization. Of the thirteen ragweed cases not sensitive to goldenrod eleven received 75 per cent or more relief from ragweed desensitization only. Of the ten ragweed cases sensitive also to goldenrod, nine received 75 per cent or more relief from ragweed desensitization alone. It therefore becomes at once obvious that even though goldenrod pollen appeared in small quantities on the plate during the ragweed season, it was not sufficiently concentrated to produce symptoms in the majority of cases. Two of the three ragweed and goldenrod sensitive cases who had received 75 per cent or less relief from ragweed desensitization alone were given coseasonal goldenrod desensitization therapy. One was promptly relieved of her remain-

ing symptoms while the other was not materially improved.

It would appear therefore that in a very heavy goldenrod year symptoms may be due to goldenrod even though there is no direct or near contact. This appeared in a heavy goldenrod year to be an unusual finding. Naturally, however, those who are known to be goldenrod sensitive must avoid close contact.

DISCUSSION

Past experience has shown that in average seasons, goldenrod sensitivity may be ignored, with the cautionary suggestion that the individual avoid close contact with the plants. In seasons in which the weed growth is heavy however it would appear that air borne goldenrod pollen may be responsible for symptoms. Certainly it is obvious that under such circumstances a ragweed sensitive individual also sensitive to goldenrod, who does not receive adequate relief from effective ragweed treatment should also receive therapeutic trial with goldenrod desensitization.

Our ideas as to how far pollen may be carried on the wind have of recent years required considerable expansion. Until recently Scheppegrell's¹ observations in the mountains of North Carolina have been the basis for the statement that ragweed pollen may carry as far as 15 miles. In 1931, however, Durham² concluded from airplane observations over Lake Michigan that ragweed pollen is nearly as concentrated 30 miles from shore as it is over the land. Black and Durham³ have reported that dry pollen may be carried as far as 100 miles in still air.

ernment study has been the authority for the statement that pollen from Alaska may be carried as far as the Northwestern United States⁴. It is therefore not at all surprising to find that we must consider it probable that the heavier pollens of insect fertilized plants may be carried in small quantities on the wind for a matter of three or four miles or more instead of the 300 or 400 feet usually allotted to them. If wingless insects are actually carried to elevations of several thou-

sand feet purely by the air currents, the surprise is that the situation under discussion is not met with more frequently.

Aside from close exposure to the plant, goldenrod sensitivity is rarely responsible for symptoms, even during years of heavy prevalence. However it would appear that this pollen may be carried in small amounts to appreciable distances by the wind and may very occasionally produce symptoms in the absence of close contact.

REFERENCES

- ¹SCHIEFFELIN, W. Hay fever and asthma, 1922, Lea & Febiger, Philadelphia.
²DUPHAM, O. C. Personal communication.
BLACK, J. H., and DUPHAM, O. C. Elm pollen as a complicating factor in hay fever, *Jr. Allergy*, 1930, 1, 501-505.
³HEALTH NEWS H-23, Apr. 25, 1931, U S P H S.
⁴TAI MAN, C. F. Air a vast carrier of living matter, *New York Times, Sci. Sect.*, 1931, Nov. 1.

The Present Status of the Ketogenic Diet

By D SCHUYLER PULFORD, M S , M D , F A C P , *Sacramento, California*

IT IS my purpose to outline the present status of the ketogenic diet rather than urge its use or disprove its value by reporting results on 75 treated cases of epilepsy. Sufficient time has now elapsed since Wilder's¹ introduction of this low carbohydrate high fat diet in 1921 to estimate its worth.

Ketosis is physiologically different from acidosis caused by a shift in acid base equilibrium and has other effects than dehydration. Therefore, in spite of the brilliant results of Fay² and McQuarrie³ and their followers with fluid restriction, diet-produced ketosis still commands our attention.

EPILEPSY A SYMPTOM NOT A DISEASE

Weed,⁴ Lennox and Cobb,⁵ Winkelman⁶ and others have advanced our knowledge of the anatomy, physiology and pathology of the central nervous system as related to convulsions so far that we now understand some of our failures to arrest epilepsy in the past. No longer is any type of epilepsy considered "idiopathic". Anatomists, physiologists, surgeons and pathologists have demonstrated conclusively the organic nature of the majority of cases studied. Dandy⁷ and others have shown at operation a "supra-cortical

laking" of fluid in the sub-arachnoid spaces not seen at autopsy because of the fall of cerebrospinal fluid pressure at death. This fluid is considered secondary to some cerebral lesion, probably an ischemia with resultant atrophy of the underlying cortex. Winkelman⁶ has demonstrated definite pathology of the arachnoid and Pacchionian bodies in eighty per cent of epileptic brains studied, be they of acute, chronic, "idiopathic", or symptomatic subjects.

Granted that all seizures are organic in origin, nevertheless physiochemical factors must explain their periodicity and the varying degree of susceptibility to such predisposing mechanical factors as hydration, increased pressure, tumors, etc. These in turn may be endocrine or even allergic in origin for all we know. But today even though we find certain organic lesions as predisposing causes we find ourselves even as in the time of Hippocrates, ignorant of the precipitating physiochemical basis of epilepsy and until this is found must believe with Doctor Fay² "That epilepsy will never be cured we are certain, but that it may be controlled in a manner similar to that we accept for diabetes is possible."

METHODS OF TREATMENT

In the evolution of the treatment of epilepsy we must not forget the

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If all epilepsy is "symptomatic" and the continuing convulsions act *per se* as constant traumata to add to the organic basis it is important to stop them early. It occurs to me that the ketogenic diet is proving a means of telling how early or extensive a change we have in the central nervous system. The ketogenic diet alone of all the methods of treatment produces an arrest in convulsions which lasts long after the ketosis is abandoned. Does this not mean that progression of the brain pathology is arrested long enough for the patient to adjust to it, and that he can adjust successfully only to a slight lesion? When dehydration is necessary either supracortical laking or advanced brain changes are present to which the patient can never adjust. Therefore, it is necessary to continue the dehydration as long as one wishes to be convulsion free.

When ketosis fails we have an advanced cerebral lesion. Dehydration should then be resorted to either alone or combined with a mild ketosis and the patient told that it will probably be a lifelong procedure.

RESULTS OF TREATMENT WITH THE KETOGENIC DIET

Helmholz¹², Peterman,¹⁷ Talbot¹⁴ and Barborka¹⁵ early showed the value of the ketogenic diet in the treatment of epilepsy. Results reported from different quarters are surprisingly uniform. Epileptic convulsions disappear completely in about one-third of all children thus treated but the proportion of arrests in adults is smaller. The convulsion free state has persisted longer after the ketogenic diet than after dehydration when the rigorous-

ness of the two regimes is lessened. Many children after returning to an almost normal diet following six months of ketosis have been apparently normal for years. In September, 1930, Helmholz¹⁶ reported a series of 272 cases started on a ketogenic diet eight years before. Of a total of 171 who cooperated completely, 43 or 30 per cent, were free from attacks for one year or more, 32 or 23 per cent were improved, and 66, or 47 per cent were not helped. Talbot¹⁴ and Peterman¹⁷ recount similar experiences. Barborka¹⁵ noted poorer results with adults. Of one hundred non-institutional, supposedly "idiopathic" cases treated with a ketogenic diet, varying from 16 to 51 years of age and of from one to thirty-two years duration he reported 12 per cent controlled, 44 per cent definitely improved and 44 per cent not benefited. Combining the controlled and the definitely improved we have 56 per cent, or over one-half of the total, benefited. My experience corroborates this report and emphasizes that we should give patients of all ages a trial treatment.

In summary, we may say that with the ketogenic diet alone, without special attention to water or mineral metabolism, one-third of the cooperative intelligent epileptics can be made free from seizures. The best results are obtained in children and young adults who are just beginning to have seizures. Patients with frequent attacks of long duration respond less favorably.

The ketogenic diet is proved to be successful with *partial* seizures. Dehydration treatment has not been tried upon this phase of epilepsy.

which are in the order of their development:

- 1 Fasting,
- 2 Ketogenic diet,
- 3 Modification of mineral metabolism—shift of acid-base equilibrium,
- 4 Modification of water metabolism—dehydration

Fasting is impracticable and became unnecessary with Wilder's introduction of the ketogenic diet in 1921. Both of these methods result in imperfect combustion of fats, producing a fatty acid acidosis. They produce a shift in the acid-base balance (preventing an abnormal alkalosis), reduce the water volume of the body, and effect in some unknown way the irritability of the central nervous system.

Since ketosis was seen to produce a shift of the acid-base equilibrium, studies were undertaken to note the effect of modifying the mineral metabolism of the body. Peterman⁸ found that alkalosis itself did not explain susceptibility to convulsions for patients made attack free by the ketogenic diet did not develop seizures on taking alkalis to the point of alkalosis. Detrick⁹ emphasized the rôle of calcium ions in both dehydrating and reducing the irritability of the body cells, a reverse action to sodium ions which help retain water in cells and increase their irritability. Sodium chloride-free diets with high calcium intake with its mobilization, if necessary, with parathormone, together with moderate fluid restriction have in her hands controlled epilepsy without the use of the strict ketogenic diet.

After fasting, ketogenic diets and the proper shift in the acid-base equi-

librium, dehydration *per se* was next advocated in the treatment of epilepsy. Fay's² dehydration reports gave a most comprehensive review of the epilepsy problem and indicate "hydration" and "dehydration" to be the most important elements of cause and cure. He concludes "The predisposing factor concerned in a major convulsive seizure is due to a hydration state, however induced, whether local or diffuse, and proper control of this factor, when possible, gives rise to an attack free existence which may continue as long as the patient's water metabolism or fluid balances remain within the limits of proper compensation."

The precipitating factor remains an unknown quantity, even as in the etiology of goiter an unknown factor still baffles us. McQuarrie's¹⁰ hydration demonstrations, the inducing of seizures by increased water intake, combined with pituitary antidiuresis, confirm the surgeons' wet brain observations, Larson and Rowntree's¹¹ water intoxication studies, and substantiate the hydration state as being the principle predisposing factor in epilepsy.

The question whether dehydration is a superior method to the strict ketogenic diet is not fairly put, for they are so closely related. The ketogenic diet adds a sedative effect to dehydration so it might be likened to a mild dehydration plus luminal. It has been said that the sedative effect of the ketogenic diet is not better than that of luminal. This is not true for it has a dehydrating effect that luminal lacks, and clinically it arrests convulsions when the luminal alone has failed.

If all epilepsy is "symptomatic" and the continuing convulsions act *per se* as constant traumata to add to the organic basis it is important to stop them early. It occurs to me that the ketogenic diet is proving a means of telling how early or extensive a change we have in the central nervous system. The ketogenic diet alone of all the methods of treatment produces an arrest in convulsions which lasts long after the ketosis is abandoned. Does this not mean that progression of the brain pathology is arrested long enough for the patient to adjust to it and that he can adjust successfully only to a slight lesion? When dehydration is necessary either supracortical laking or advanced brain changes are present to which the patient can never adjust. Therefore, it is necessary to continue the dehydration as long as one wishes to be convulsion free.

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The ketogenic diet is proven to be successful with *febrile convulsions*. This treatment has to be continued upon this phase of therapy.

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The ketogenic diet is relatively successful with patients who do not respond to treatment by other means. It is upon this phase of epilepsy

MODERN METHOD OF TREATMENT

It has been my experience that for the successful handling of the epileptic symptom complex one cannot rely solely upon the ketogenic diet. Quite often ketosis must be supplemented by low NaCl, high calcium, intake and limitation of fluids. I have called back several patients who were only improved on a ketogenic diet alone, who with this combination treatment are now convulsion free. Each of the above methods, ketosis, sodium-calcium change and dehydration will arrest certain patients. Many of them need a combination of two or three of these systems of treatment. McQuarrie¹⁰ is in accord with this experience and Bauer¹⁹ placed 27 children who showed only 35 per cent cures with the ketogenic diet on Fay's method of dehydration with the result that "the same group over a period of one year under control showed almost 100 per cent symptomatic relief of attacks." Helmholz¹⁶ patients not helped by withdrawal of water when a ketogenic diet failed, were not reported in detail and may belong to the group which needs all three methods to arrest convulsions. Perhaps they even fall into the class of Howard West's²⁰ case of an epileptic child with an associated diabetes who even with impending diabetic coma with a low plasma carbon dioxide figure continued to have seizures. This case stands as a shining example of one of the 35 per cent of cases which ketogenic diet does not cure, probably because of an advanced organic brain lesion. Such an isolated experience should not discourage one from continuing with the ketogenic diet treatment but empha-

sizes the necessity of combining the newer methods with it.

It is often found practicable to give from one to three grains of luminal a day in the early stages of treatment though this is not always necessary. When stopping it, it should be withdrawn gradually.

CAUSES FOR FAILURE

Early epilepsy, particularly *petit mal*, apparently can be cured, *grand mal* when well established can be arrested, not cured. Advanced organic brain changes are the chief causes preventing successful treatment.

If there is a removable focal organic brain tumor, operation should not be delayed. Parker²¹ reported that in a series of 313 brain tumor cases seven per cent had no other symptom than convulsions for over a year. Twenty-one per cent had convulsions some time in their course, and a convulsion was the initial symptom in over half of these. Advanced degenerative organic lesions in the Pacchionian system or cortex, and developmental venous anomalies often defy treatment. A complete neurological examination including x-rays of the skull and ventriculograms should therefore be done on all convulsion cases.

Old age, chronicity, mental deterioration, psychopathies, and lack of intelligence or cooperative ability spell failure in direct proportion to their extent. Good physical and mental hygiene without the factors of fatigue and emotional stress and worry are essential. Mechanical factors such as mistakes in calculations, variation in foods, too little explanation to the patient, too small a degree of ketosis,

etc., must be considered. It is often necessary to increase the degree of ketosis over that necessary to give a slightly positive diacetic acid test in the urine. A fluctuation in the degree of ketosis may be due to an individual variation in the absorption of fat in different persons. When a high degree of ketosis fails, further water restriction or a change in the mineral metabolism should be effected.

DANGERS OF THE KETOGENIC DIET

Since the including of yeast and viosterol in the ketogenic diet, no deficiency diseases have been reported. No harm has been reported from a negative nitrogen balance which, if present on the low protein intakes used, is only transitory. Whether the two grams protein per kilogram of body weight as recommended by McQuairie²² are necessary, or the one and one-fourth grams as usually given to growing children, sufficient, is not settled. Adults seem to do well on two-thirds of a gram of protein per kilogram body weight as Wilder has proven with diabetic diets. It is customary now to give calcium lactate to prevent the tendency to a negative calcium balance which high fat diets invoke, as well as for its dehydrating and sedative effects. In this regard it should be noted that calcium lactate $\text{Ca}(\text{C}_6\text{H}_7\text{O}_7)_2 \cdot 5 \text{H}_2\text{O}$ with a molecular weight of 308 in the process of metabolism gives an available glucose, $\text{C}_6\text{H}_{12}\text{O}_6$, molecule of 180. This means that the eight grams of calcium lactate which is often prescribed daily would develop in its metabolism 4.67 of anti-ketogenic glucose.

The hypercholesteremia of high fat diets has yet to be proved deleterious with epileptics as Joslin²³ holds it is

for diabetics. So with the giving of brewer's yeast, viosterol, and calcium lactate with the ketogenic diet, and with water restriction to twenty ounces the deeper states of ketosis are not often necessary to control convulsions and a sufficient supply of nitrogen and an unharmed amount of fat are consumed. Amenorrhea in women is prevented by the vitamin B of brewer's yeast.

THERAPEUTIC APPLICATIONS OTHER THAN EPILEPSY

It is common knowledge that the high fat diet, through its high vitamin A content, reduces the number and severity of infections such as colds and influenza. Prevention or attenuation of measles and scarlet fever is also noted. Higgins²⁴ has suggested that because of the lessened fecal bacterial content the ketogenic diet should be tried in arthritis or other diseases thought to be due to absorption from the colon. Clark²⁵ and Helmholz²⁶ have unpublished data to show the ketogenic diet to be a distinct adjunct in the treatment of certain types of urinary infection.

Wolbach and Howe²⁷ of Harvard, on animal experimentation, concluded that vitamin A deficiency allows injury to all epithelial structures, parts of the respiratory, alimentary, genitourinary systems, and the cutaneous, and that the high vitamin A content of the ketogenic diet tends to strengthen this defense against bacterial invasion.

Migraine headaches have been treated with about the same degree of success as the epilepsies with the ketogenic diet. A few cases of asthma have also been benefited. Helwig²⁸ has suggested that the ketogenic diet

MODERN METHOD OF TREATMENT

It has been my experience that for the successful handling of the epileptic symptom complex one cannot rely solely upon the ketogenic diet. Quite often ketosis must be supplemented by low NaCl, high calcium, intake and limitation of fluids. I have called back several patients who were only improved on a ketogenic diet alone, who with this combination treatment are now convulsion free. Each of the above methods, ketosis, sodium-calcium change and dehydration will arrest certain patients. Many of them need a combination of two or three of these systems of treatment. McQuarrie¹⁰ is in accord with this experience and Bauer¹⁹ placed 27 children who showed only 35 per cent cures with the ketogenic diet on Fay's method of dehydration with the result that "the same group over a period of one year under control showed almost 100 per cent symptomatic relief of attacks." Helmholtz¹⁶ patients not helped by withdrawal of water when a ketogenic diet failed, were not reported in detail and may belong to the group which needs all three methods to arrest convulsions. Perhaps they even fall into the class of Howard West's²⁰ case of an epileptic child with an associated diabetes who even with impending diabetic coma with a low plasma carbon dioxide figure continued to have seizures. This case stands as a shining example of one of the 35 per cent of cases which ketogenic diet does not cure, probably because of an advanced organic brain lesion. Such an isolated experience should not discourage one from continuing with the ketogenic diet treatment but empha-

sizes the necessity of combining the newer methods with it.

It is often found practicable to give from one to three grains of luminal a day in the early stages of treatment though this is not always necessary. When stopping it, it should be withdrawn gradually.

CAUSES FOR FAILURE

Early epilepsy, particularly *petit mal*, apparently can be cured, *grand mal* when well established can be arrested, not cured. Advanced organic brain changes are the chief causes preventing successful treatment.

If there is a removable focal organic brain tumor, operation should not be delayed. Parker²¹ reported that in a series of 313 brain tumor cases seven per cent had no other symptom than convulsions for over a year. Twenty-one per cent had convulsions some time in their course, and a convulsion was the initial symptom in over half of these. Advanced degenerative organic lesions in the Pacchionian system or cortex, and developmental venous anomalies often defy treatment. A complete neurological examination including x-rays of the skull and ventriculograms should therefore be done on all convulsion cases.

Old age, chronicity, mental deterioration, psychopathies, and lack of intelligence or cooperative ability spell failure in direct proportion to their extent. Good physical and mental hygiene without the factors of fatigue and emotional stress and worry are essential. Mechanical factors such as mistakes in calculations, variation in foods, too little explanation to the patient, too small a degree of ketosis,

etc. must be considered. It is often necessary to increase the degree of ketosis over that necessary to give a slightly positive diacetic acid test in the urine. A fluctuation in the degree of ketosis may be due to an individual variation in the absorption of fat in different persons. When a high degree of ketosis fails further water restriction or a change in the mineral metabolism should be effected.

DANGERS OF THE KETOGENIC DIET

Since the including of yeast and cholesterol in the ketogenic diet, no deficiency diseases have been reported. No harm has been reported from a negative nitrogen balance which, if present on the low protein intakes used, is only transitory. Whether the two grams protein per kilogram of body weight as recommended by McQuarrie²² are necessary or the one and one-fourth grams as usually given to growing children sufficient, is not settled. Adults seem to do well on two-thirds of a gram of protein per kilogram body weight, as Wilder has proven with diabetic diets. It is customary now to give calcium lactate to prevent the tendency to a negative calcium balance which high fat diets invoke as well as for its dehydrating and sedative effects. In this regard it should be noted that calcium lactate $\text{Ca}(\text{C}_6\text{H}_5\text{O}_2)_2 \cdot 5 \text{H}_2\text{O}$ with a molecular weight of 308 in the process of metabolism gives an available glucose, $\text{C}_6\text{H}_{12}\text{O}_6$ molecule of 180. This means that the eight grams of calcium lactate which is often prescribed daily would develop in its metabolism 4.67 of anti-ketogenic glucose.

The hypercholesterolemia of high fat diets has yet to be proved deleterious with epileptics as Joslin²³ holds it is

for diabetics. So with the giving of brewer's yeast, cholesterol, and calcium lactate with the ketogenic diet, and with water restriction to twenty ounces the deeper states of ketosis are not often necessary to control convulsions and a sufficient supply of nitrogen and an unharmed amount of fat are consumed. Amenorrhea in women is prevented by the vitamin B of brewer's yeast.

THERAPEUTIC APPLICATIONS OTHER THAN EPILEPSY

It is common knowledge that the high fat diet, through its high vitamin A content, reduces the number and severity of infections such as colds and influenza. Prevention or attenuation of measles and scarlet fever is also noted. Higgins²⁴ has suggested that because of the lessened fecal bacterial content the ketogenic diet should be tried in arthritis or other diseases thought to be due to absorption from the colon. Clark²⁵ and Helmholtz²⁶ have unpublished data to show the ketogenic diet to be a distinct adjunct in the treatment of certain types of urinary infection.

Wolbach and Howe²⁷ of Harvard on animal experimentation, concluded that vitamin A deficiency allows injury to all epithelial structures, namely of the respiratory, alimentary, genito-urinary systems and the eye and skin and that the high vitamin A content of the ketogenic diet tends to strengthen this defense lining against bacterial invasion.

Migraine headache has been cured with about the same proportion of success as the epileptic cases in which a few cases of asthmatic cough have been benefited. These last two are suggestive, allergy is the common factor.

lepsy Rather would we say that the shift in acid-base equilibrium of the body fluids was a predisposing cause to both the phenomena of "allergy" and epilepsy

It seems logical to treat all post-traumatic head injuries by some method of dehydration to prevent later complications such as epilepsy for permanent nerve changes can be initiated by a few hours intracranial pressure and its consequent anoxemia

We see, then, that the ketogenic diet has been found a useful adjunct in the treatment of

- 1 Migraine,
- 2 Asthma,
- 3 Infections of the urinary tract, and
- 4 As a prophylactic against the common acute infections and infectious diseases

SUMMARY

1 Ketogenic diet ketosis acts differently physiologically from acidosis caused by a shift in acid-base equilibrium, and has other effects than dehydration The ketogenic diet is still necessary, therefore, in the treatment of epilepsy

2 In the light of the studies of the last decade we must consider all epilepsy as symptomatic from organic changes in the central nervous system, and not "idiopathic"

3 Until the "precipitating cause", thought to be some physiochemical state, is discovered its cure is not possible The arrest of convulsions is obtained, however, in the majority of cases under controlled conditions of ketosis, sodium chloride-calcium ion balance and water balance

4 The results reported from the use of the ketogenic diet alone without

special attention to the water or mineral metabolism are surprisingly uniform About one-third of the intelligent, cooperative epileptics can be arrested, another one-third are benefited so that they wish to continue with the diet, but one-third are not helped Those that are benefited have only slight lesions

5 The ketogenic diet stops *petit mal* definitely in many early cases, dehydration not benefiting these patients *Petit mal* is, therefore, the one phase of epilepsy that may be cured

6 The modern method of treating epilepsy with a combination of ketogenic diet, dehydration and shift in the sodium-calcium ions arrests convulsions in the majority of cases A "cure", however, is no nearer now than in 1921, when the ketogenic diet was first introduced

7 The chief causes for failure are brain tumor, mental deterioration due to chronicity and old age, psychopathic states and lack of cooperation

8 The dangers inherent in the ketogenic diet such as nitrogen, calcium, and vitamin deficiency are controverted by yeast, viosterol, and calcium intake sufficient to prevent pellagra, amenorrhea, and negative nitrogen and calcium balance Fluid restriction permits a mild ketosis without a high degree of cholesteremia formerly found with a stricter ketogenic diet

9 The ketogenic diet has been found a useful adjunct in the treatment of migraine headache, asthma and urinary infections, and, in the persons who are receiving it, it acts as a prophylactic against the common acute respiratory infections such as colds and influenza as well as the acute infectious diseases of childhood

REFERENCES

- ¹WILDER, R M The effects of ketonuria on the course of epilepsy, *Mayo Clin Bull*, 1921, **11**, 307
- ²FAY, T Epilepsy, clinical observations on the control of convulsive seizures by means of dehydration, *Jr Nerv and Ment Dis*, 1930, **1XXI**, 481-633
- ³MCQUARRIE, I, MANCHESTER, R C, and HUSTED, C The effect of induced changes in the state of hydration upon the occurrence of seizures in epileptic children, *Assoc Res Nerv and Ment Dis*, 1931, **VII**, Part II, 623-637
- ⁴WEED, L H Experimental studies of intracranial pressure, *Assoc Res Nerv and Ment Dis*, 1929, **VIII**, Part I, 25-67
- ⁵LENNOW, W G, and COBB, S Relation of certain physiochemical processes to epileptiform seizures, *Am Jr Psychiat*, 1929, **VIII**, 837-847
- ⁶WINKELMAN, N W Pathological studies of the Pacchionian bodies in various types of the convulsive state, *Assoc Res Nerv and Ment Dis*, 1931, **VII**, Part II 502-519
- ⁷DANDY, W E Impressions of the pathology of epilepsy from operations, *Am Jr Psychiat*, 1927, **11** 519-522
- ⁸PETERMAN, W G Discussion, *Am Psychiat Assoc*, Atlanta, Ga, May 14, 1929
- ⁹DETRICK, H H Epilepsy with regard to the influence of calcium and water metabolism upon the incidence of seizures, *Calif and West Med*, 1931, **XXIV**, 240-246
- ¹⁰MCQUARRIE, I, and PEFLER, D B The effects of sustained pituitary antidiuresis and forced water drinking in epileptic children, a diagnostic and etiologic study, *Jr Clin Invest* 1931 **10**, 915-940
- ¹¹ROWANTREFF, L G Effects on mammals of administration of excessive quantities of water, *Jr Pharmacol and Exper Therap* 1926 **XXX** 135-159
- ¹²HELMHOLTZ, H F Treatment of epilepsy in childhood five years experience with ketogenic diet, *Jr Am Med Assoc* 1927 **LXXXIII**, 2028-2032
- ¹³PETERMAN, W G Ketogenic diet in treatment of epilepsy, *Am Jr Dis Child*, 1924, **XXVIII**, 28-33
- ¹⁴TALBOT, F B, MERCALF, K M, and MORIARTY, M A clinical study of epileptic children treated by ketogenic diet, *Boston Med and Surg Jr*, 1927, **CXCVI**, 89-96
- ¹⁵BARBORKA, C J Results of treatment by ketogenic diet in one hundred cases of epilepsy in adults, *Assoc Res Nerv and Ment Dis*, 1929, **VI**, Part II, 638-658
- ¹⁶HELMHOLTZ, H F, and KEITH, H M Eight years' experience with ketogenic diet in the treatment of epilepsy, *Jr Am Med Assoc*, 1930, **XCIV**, 707-709
- ¹⁷PETERMAN, W G Ketogenic diet *Jr Am Med Assoc*, 1928, **XC**, 1427-1429
- ¹⁸BARBORKA, C J Epilepsy in adults Results of treatment by ketogenic diet in one hundred cases *Arch Neurol and Psychiat* 1930, **XXIII**, 904-914
- ¹⁹BALFE, E L Management of epilepsy with special reference to diet *Pennsylvania Med Jr* 1929 **XXXIII** 690-692
- ²⁰WEST, H Personal communication
- ²¹PARKER, H L The relationship of epileptic seizures to brain tumor, *Minnesota Med* 1931 **XIV**, 245
- ²²MCQUARRIE, I Epilepsy in children The relationship of water balance to the occurrence of seizures *Am Jr Dis Child* 1929 **XXXIII**, 451-567
- ²³JOSLIN, E P Arteriosclerosis in diabetes *Ann Int Med* 1930 **IV**, 54-60
- ²⁴HIGGINS, H L Some physiological and clinical effects of high fat feeding *New England Jr Med*, 1930 **CCXII** 145-151
- ²⁵CLARK, A I *Escherichia coli* bacteremia under ketogenic treatment *Proc Soc Med Met Mayo Clin* 1931 **1**, 42-45
- ²⁶HELMHOLTZ, H F The long term effects of the treatment of paroxysmal epilepsy with anomalies of the central nervous system *Stat Med Mayo Clin* 1931 **1**, 41-60
- ²⁷WELFACH and HOWARD *Jr Dis Child* 1931 **XXXV**, 1-15

The Treatment of Cavities in Pulmonary Tuberculosis

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AFTER observing tuberculosis clinically for the past 26 years, you can hardly blame me for not becoming overly enthusiastic when some optimist suggests the expectant treatment of cavities, claiming that nature, with the aid of bed rest, hard pillows and plenty of endurance, will effect a result as often as those of us who advocate interference by means of various forms of compression therapy

We have had the curability of tuberculosis sung from the housetops over so long a period of time that many medical men really delude themselves into thinking that it is a curable disease To disabuse yourself, you need but scan the statistics gathered by competent men the world over True, when the disease is diagnosed early and proper advice given, the majority of those patients get well However, early diagnosis is a rarity as is evidenced by the fact that sanatoria over the country show the large percentage of their patients in the moderately advanced and the far advanced stages of the disease

Let us then face facts and not fancies We deal with a clinical entity and not a supposition contrary to fact

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When tuberculosis passes the early stage, cavitation occurs in the majority of patients, evidenced either by physical signs or x-ray examination It may be present also in early tuberculosis, when the onset has been acute and the process exudative But cavities are cavities, and should instill into the minds of the tuberculosis worker a wholesome respect for their presence, and a well grounded desire for their elimination They are all too dangerous and the sooner we realize the possibilities of aspiration extension, hemorrhage and miliary spread, and then act upon the realization, the more we shall be doing to restore the health of an otherwise probably doomed consumptive We are too prone to remember the patient who lived for 20 years with an open cavity, and forget the hundreds who are dead within 15 months of the time the cavity was diagnosed Clinical impressions may have their place in medicine, although I doubt it, but facts form a much saner basis for successful treatment of disease

The pathologist has worked out various types of cavities and has shown how and why healing takes place He can tell you which cavities nature will heal and why nature can effect a result He knows from the appearance of

the wall whether or not we can expect a collapse of a given cavity. He can tell you from the location in the lung whether mechanical interference is necessary or whether magic will do the trick. He has converted many clinicians who feel the urge to play a game of watchful waiting to see what an all-wise Providence may or may not do. I admit that small grape-skinned cavities situated beneath the clavicle offer better chances of spontaneous healing than large thick-walled cavities in a more mobile part of the lung. I also admit that nature at times performs marvelous feats, but I am cognizant also of the fact that she has made many failures.

Then, too, we must not lose sight of the fact that an economic problem is involved. Most patients can ill afford years of cure-chasing when some simple procedure may restore health in months rather than years. Since the depression, the world is full of the new poor, a situation which makes active resistance rather than passive doubly advantageous.

In glancing over the literature written by advocates of the watchful waiting policy, I cannot let pass unchallenged the article by Fales and Beaudet.¹ These authors claim better results by means of bed rest than I have been able to attain by compression therapy. They show healing in 66 per cent of small cavities, 23 per cent of large cavities, and 32 per cent of cases with multiple cavities, or an average healing of 40 per cent in all types. They chose to compare these figures with my percentages published in 1929² before intrapleural pneumolysis increased the averages markedly. Published reports

of my work³ were available at the time they made use of the less favorable figures. They elected to show that 39 per cent of my cases gave complete collapse by pneumothorax, and inferred that this was the end result in cavity healing. They should have averaged the percentage of healed cases in complete collapse, or 53 per cent, and the healed thoracoplasties, or 36 per cent, making a total of 45 per cent of healed cavities. The later statistics to which they did not refer, increase this to 57 per cent. In other words, compression therapy shows healing of cavities in 57 per cent of cases, and rest shows healing in 40 per cent—a 17 per cent advantage for compression treatment. Then, too, they forgot that the class of cases we treat shows large or multiple cavitation in the majority of patients, and that this class is the least benefited by the rest regime. They also attempted by combining the group in which cavities that are healed and that in which they are made smaller to make the results show to better advantage. Unless cavities are healed, they are still a grave menace, and no apologies should be offered for allowing them to remain open.

In an analysis of 700 cases of artificial pneumothorax,² I showed the following results:

Complete compression
53% well 24% dead
Partial compression
25% well 44% dead
No free space
16% well 60% dead

A glance at these percentages shows conclusively that closure of cavities pays, since the complete compression cases with cavities closed show 53 per

cent well and 24 per cent dead, and the "no free space" cases—the ones on whom it was impossible to do a pneumothorax—show 16 per cent well and 60 per cent dead. These same failures were of necessity treated by bed rest. There was nothing else to do.

Many partial compressions are now made complete by intrapleural pneumolysis, and many of the pneumothorax failures are being given the benefit of extrapleural pneumolysis or thoracoplasty. In fact, everything is being done to eliminate the cavity.

I like Pinner's classification of cavities since it is simple and practical. He divides them into (1) honeycombing or multiple small cavities, (2) small round or slightly oval cavities with or without perifocal change, (3) irregular shaped cavities with thick walls. The second type offers best chances for compression therapy, although honeycomb areas collapse if not too near the apex where the lung is usually firmly adherent. The irregular shaped cavity with thick walls is hardest to collapse, and yet many times perseverance wins.

Let me here outline the various methods and their indications. First of all rest is utilized to see what the patient can do with small cavities or honeycomb areas. Enough cavities heal spontaneously to warrant this expectant treatment for a reasonable length of time, but for a reasonable length of time *only*. This period should be put at three months, and then if no attempt at healing has taken place, institute at once some form of compression.

Phrenicectomy is the method of choice in small round cavities with thin walls, the so-called grape-skin type. No matter where situated, this

form of compression should be tried first. Then if collapse is not attained, a pneumothorax may be attempted. The fact that a phrenicectomy has been done is no barrier to pneumothorax treatment—oftentimes it is an aid. This, too, is the method of choice when pneumothorax has proven a failure before resorting to extrapleural pneumolysis or to thoracoplasty.

Pneumothorax is by far the most satisfactory form of compression therapy in the majority of cases, and should be the method of choice when phrenicectomy fails, or in the cases showing multiple cavitation or large cavities with thick walls. After two or three months, if adhesions prevent the closure of the cavity, intrapleural pneumolysis, if feasible, should at once be attempted. This procedure converts many partial collapse cases into complete collapse, with resultant cavity closure.

Many cavities—situated in the upper third of the lung where adhesions cannot be burned—are suitable for extrapleural pneumolysis. This is fairly successful when the lung is held firmly from below by a pneumothorax or when adhesions are dense so that when paraffin is implanted the lung does not slip away thus defeating the purpose of the paraffin pressure.

Thoracoplasty falls next in methods of choice. The longer we are in this work, the more prone we are to do everything possible before resorting to radical surgery. More and more patients are given the benefit of pneumothorax, and less and less thoracoplasty. When proper selection is made and all other methods have failed, this surgical procedure proves effective and should

by all means be advised. Our results show 36 per cent made well but also 42 per cent dead over the years, and this is due to the fact that tuberculous patients are poor surgical risks at best, and thoracoplasty is *major* surgery.

Intelligent physicians should recognize the necessity of conservatism. Fads must be thrown into the discard at once, but progress in the treatment of disease can come only when we prof-

it by experience and learn to evaluate our own work and that of others. The man who temporizes with tuberculosis today, who treats advanced disease by bed rest alone, and the usual routine of twenty-five years ago, failing to utilize the methods of compression therapy at his command, is a menace to his patients, and is not giving the best the profession has to offer in the treatment of this disease.

REFERENCES

¹FALES, L. H., and BEAUDET, E. A. The healing of tuberculous cavities, *Am Rev Tuberc*, 1931, xxiii, 690-701.

²PETERS, L. S. Compression therapy of pulmonary tuberculosis, comparative study,

Am Rev Tuberc, 1929, xix, 74-83.

PETERS, L. S., and CORVISH, P. G. JR. Intrapleural pneumolysis by Jacobaeus-Unverricht method, *Med Jr and Rec*, 1930, cxxxii, 265-269.

Chronic Invalidism with Marked Personality Changes Due to Myxedema

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THE clinical aspect of myxedema was presented with such thoroughness by the special committee of the Clinical Society of London appointed in 1883 to study this disease that little if anything has been added to the clinical picture since that time. Among the 109 cases reviewed, it was found that slowness of thought and mental disorders of an irritable and suspicious character, with hebétude alternating with somnolence, were very common. Delusions and hallucinations occurred in one-half the cases and insanity was noted in about the same per cent. Acute or chronic mania and dementia were common with a marked predominance of suspicion and self-accusation.

Since the advent of simple apparatus for determining the basal metabolism, the condition is frequently detected, especially in hospitals and clinics where routine tests are performed. Yet the disease is often undetected for many years as the cases here presented illustrate.

One is impressed with the marked personality changes present in the advanced cases: irritability, untruthfulness, suspicion, delusions, retarded

cerebration, inability to concentrate, introversion and failing memory are conspicuous in the cases here reported. It is quite obvious that these patients are very difficult to get on with and as they frequently live many years, the home is sometimes wrecked as a consequence.

CASE REPORTS

Case I Nearly every pleasant afternoon after banking hours some twenty years ago, one could see a fine-looking old gentleman with closely cropped beard sitting in a buggy with the top thrown back, driving a rangy bay horse about the streets of Hartford. On the seat beside him was what to a casual observer might easily have been mistaken for an image of Buddha. The sallow, brown skin, the puffy, expressionless face and the sinister appearance in general, resembled closely the image of the great god. Whenever I saw them I was deeply interested because a few years before, while an intern in the Hartford Hospital, this woman, the wife of the banker, had been a patient of mine suffering from a badly infected arm. Her appearance at that time was essentially the same.

The arm healed slowly and as she was rather concerned about the fact that her hair was falling, I prescribed a "hair tonic." Her appearance suggested nephritis but a careful study did not reveal any renal lesions. Her speech was slow and monotonous. Everyone thought her "queer", however because of her universal suspicion of much of the treatment. It was very difficult to have her take her medicine as she was sure

she was being poisoned and surreptitiously she would telephone her husband to tell him she was sure she was being given poison. We then learned that for a long time she had acted queerly and had grown increasingly suspicious. That her symptoms were due to lack of thyroid secretion never occurred to any of us.

Some years later she came under the care of Dr I W Kingsbury who recognized the condition and attempted to administer thyroid. She was so psychotic however that she never could be made to take medicine with any regularity and consequently few, if any, beneficial results were obtained. A large part of her husband's life was spent in a futile endeavor to have her recover her health. There was no such thing as family life; the children grew up without the usual mother's solicitude and guidance and the family was all but wrecked, due to her years of invalidism.

Case II Shortly after the war, I used to see about the streets a man of middle age whose appearance fascinated me. He was about medium height, stocky and thick-set. He had a distinct pallor combined with a bloated appearance of the face and he was bald except for a few wisps of hair, here and there, that appeared to have sufficient tenacity to remain in place.

He walked with a plodding gait, lifting his feet but little above the sidewalk. When getting aboard a trolley car he would lurch forward and was able to get on only with great difficulty. As I subsequently learned, when going upstairs at home he would have to go up on his hands and knees.

He consulted me in July, 1919, complaining of weakness, shortness of breath and awkwardness in his movements. He also suffered from bleeding hemorrhoids, a not uncommon complication of myxedema. Because of his clumsiness in getting about and working, he was forced to give up a lucrative position in a shop as he no longer was sufficiently deft. He had recently attempted to support himself as an itinerant salesman of barber supplies. From his wife I obtained the following information:

"Until he was 26 years of age he had a good position in a shop and worked steadily



FIG 1 Case II Taken in 1900, before appearance of symptoms of myxedema. Note alert expression of eyes.

He was of a jolly, buoyant disposition and lived happily with his wife. When about 26, twenty-seven years prior to my seeing him, he began to have difficulty in doing his work as rapidly as hitherto. At 34 he had what was probably an abscess of the lung from which he made a good recovery. However thereafter he was able to carry on his work only with a great deal of assistance. He would outline a definite plan of action involving a large number of details that would require several days to consummate, if I did not watch him", said his wife, "and make out orders and keep track of everything connected with the business. When he was about half through, he would get things all mixed up so that he did not seem to remember when I tried to tell him what his first plans were. He was in poor health all the time and under some doctor's care most of the time. He began to grow stout but it seemed more like bloat than healthy flesh. He was in this condition for several years. The doctors consulted told him they could find no serious trouble but he seemed to grow fat. He grew a mature old man. About seven years ago I was positive that he had some trouble for he seemed changed in every way. Others did not notice this until I told them."



FIG 2 Case II Taken about 1905 The tissues of the face have a thick puffy appearance and the lack of lines of expression is apparent

my women friends began to tell me that he had changed so much in his actions that they did not like to be left alone with him. About this time his attitude with regard to sexual relations towards me changed very definitely. He had hitherto been very considerate but now his demands were very excessive, so that I never remained alone in the room with him. At about this time there was a distinct change in his disposition. He had always been good-natured but now he began to fly into a temper over trifles and to appear to think I wished to get rid of him. He became very suspicious, especially when anyone was talking where he could not hear what was being said, as he was sure they were saying derogatory things about him. He refused to take medicine or even food unless I took some and he became very despondent.

He had spells that were like fainting, although he did not lose consciousness, he would fall down and be perfectly still and at other times he would have a very stupid expression. He had been having these 'spells' for the past eight years.

About two years before I saw him, his hair began to grow thin. At no time in his life had he ever perspired normally and he felt the cold extremely, in fact he remarked that it was the joke of the family because he was so cold. Photographs taken in 1900, when he was 18 years old, showed him as an alert individual. Those taken during subsequent years showed a distinct change in appearance, a bloated condition of the face and complete loss of all expression until finally, just before I saw him, his expression had lost all resemblance to that of a human being and his countenance was bestial.

It was not possible to have a basal metabolism test made at this time, but he was immediately put upon thyroid with most dramatic results. Within a month after treatment was started, his speech became very much more rapid, his ideas came more easily and there was a marked improvement in his ability to walk. For the first time in his life he began to perspire. Soon his head was covered with fine soft hair except for a small spot in the back where the hair usually becomes thin past middle age. He was no longer recognized by his former patrons, in fact, one barber asked him what had become



FIG 3 Case II Taken at the conclusion of treatment after patient has resumed his work. Note the alert expression.

of the other fellow who used to visit him with the barber supplies. Before long, he returned to his occupation as an expert tool-maker where great skill and accuracy are required and he was rated as the best workman in the room of thirty.

The noteworthy points were the apparent good health up to the age of 26 years, notwithstanding the fact that the thyroid was functioning at a somewhat low level as evidenced by the fact that the patient never perspired, the gradual development of symptoms following an acute illness, the slowing up of mental processes, the development of delusions, attacks of unconsciousness, loss of a lucrative position and the almost complete breaking up of the family as his wife had been urged by friends to secure a divorce. Finally, the complete restoration to health following thyroid administration after over twenty years of semi-invalidism.

Case III A few years ago I was asked to see a woman of 70 years of age who was considered by her neighbors to be "not right" mentally and by her family as "bordering on insanity." For five years previously she had been in very poor health and for three years confined to her home by reason of weakness. She complained much of pain in the back of her head and neck, apparently following an attack of herpes zoster three years before. There had also been attacks of pain suggestive of gall bladder disease. She felt the cold intensely and complained so bitterly that the house had to be kept so hot that the other members of the family could scarcely stand it. As a child and young woman she did not perspire.

She exhibited poor judgment in meeting the events of everyday life and was most unreasonable, combative and difficult to get on with. She would repeat things over and over many times and was extremely egocentric. A grown daughter who was in business

always dreaded returning home from the office because of her mother's irritability. The patient's husband, just before his death a few years previously, told his daughter she would have need of all the patience she could muster to stand her mother's constant nagging and faultfinding.

Shortly before I saw her, some lay friend suggested that she might have myxedema, as a relative who had had this malady presented similar complaints and accordingly thyroid administration had been started without, however, any material change at that time. She presented a bloated expression with pallor of the mucous membranes, no axillary or pubic hair, the skin though bloated was somewhat wrinkled in places and very dry. Speech was slow and thick as though the tongue were swollen. Tactile and pain sense seemed to be much diminished over the legs, knee jerks were normal, the ankle jerks were not tested. She had a rather marked secondary anemia. With the improvement following thyroid administration, the change in her voice was so marked that it was not recognized over the telephone. (This occurred in another case not here reported.) Her daughter subsequently wrote me that she was a different person from the woman she had known all her life.

Case IV Three years ago, there was admitted to my service at the Hartford Hospital, a middle-aged woman complaining of nervousness. It was very difficult to obtain a history from her as she seemed confused. She stated that nine years previously she had a child that died at birth. She worried a good deal and felt that her illness dated from this time. From her son-in-law it was learned that when he first knew her ten years previously she was a strong, healthy woman, energetic, ambitious, doing all of her housework, not complaining or manifesting signs of nervousness. He had noted a marked change during the past few years. She became quite garrulous and her chief conversation was concerning her illness, the aches and pains which she felt generally in her body. At times she was so restless and nervous that she could not sleep. She dreamed of being in a dark, cold, and lonely place, and she would wake up in the middle of the night, feeling as though she were in a dark, cold, and lonely place, and she would cry out for help.

down much during the day. More and more she has neglected her housework so that she does very little. Occasionally she will start off with considerable energy but promptly becomes very tired and has to stop and rest. She is very easily upset about trivialities, as for instance, when her husband would ask her if a certain bill had been paid, she would break into tears and cry for a long time. She appears very slow in understanding and requires a long time to answer questions. Walking up to the store, a short distance from her home, she becomes very tired and on her return is completely exhausted. As he expressed it, "She has not been easy to live with and has not accomplished much in her housework."

Many physicians had been consulted and much medication prescribed apparently, however, without any real improvement. One physician whom she had consulted every few weeks for the past few years stated that he was giving her medicine which would help her "low blood." Six months before entering

the hospital, her teeth were all removed. Because of the pains in her feet she had x-rays taken and special shoes made but they did not relieve the pain nor improve the numbness in her legs. At all times she complains of feeling the cold very acutely and in hot weather never perspires. Finally, as she expressed it she "did not know whether she was going or coming." Confidentially she explained that she was sure there was pus still in the sockets of her teeth which were removed and this undoubtedly was caused by the "poisoned pills" which her previous physician had given her. She frequently referred during the early part of her sickness to the "poisoned medicine" that her doctor had given her.

It was difficult for me to realize that this sallow-complexioned woman with expressionless, bloated face and sluggish mentality was the same individual who 15 years before was an alert, bright and capable waitress in a restaurant where I often had lunch, but such was the case. The basal metabolic rate was



FIG. 4. Case IV. 'A' was taken before treatment and 'B' three months after treatment had been started. Note in the latter the absence of supraclavicular pads and of thickness of the neck. There has been also a marked change in the appearance of the hands and in the texture of the skin.

—43 She was given three grains of thyroid a day and the rate reached normal 15 days after the thyroid was started, only 56 grains in all being required to bring about the remarkable transformation

For the past three years she has been taking from two to three grains of thyroid daily, the metabolic rate varying from —5 to —20, according to the amount of thyroid, but no detectable clinical change accompanies the change in rate

Case V A woman of 69 consulted Dr Alexander Prince in February, 1923, because of failing vision. He was immediately impressed with her appearance and, suspecting that she had myxedema, sent her to me for examination and basal metabolism estimation. In addition to her poor vision, she had had "a cold feeling" for two years and for the past year this had been much worse. Her last child was born when she was 35. This

was followed by the menopause and since that time she had been in poor health. The first symptom noticed was the sensitiveness to cold and what she described as "choking spells". For years her speech had been thick, but this thickness has increased and now is accompanied by hesitation. Her memory is poor. For years she has not perspired. Especially distressing has been what she refers to as a numb feeling through her knees and at times they ache a great deal. Following the death of the child referred to, 24 years ago, her hair began to fall. Severe headaches were helped somewhat by glasses. She has become weak though gaining in weight, and has become exceedingly suspicious. She was rather pale, with puffy, expressionless face and exhibited a slight rocking of the head from side to side. The lower lip was thick, the speech slow and difficult to understand, the skin was dry. The basal

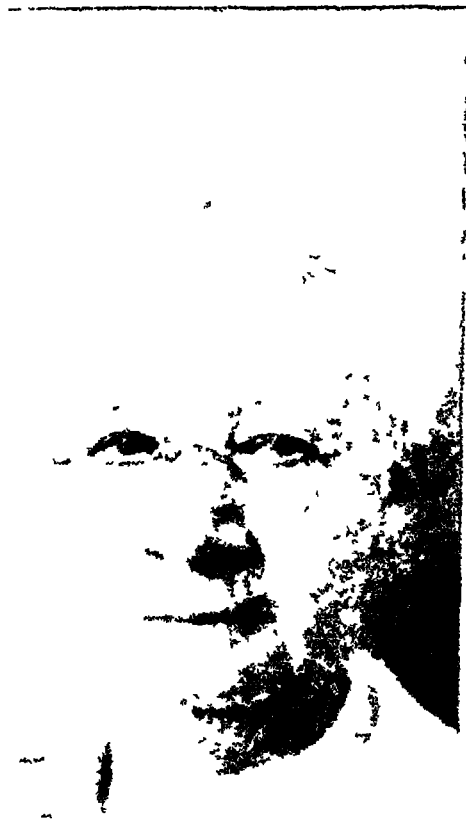
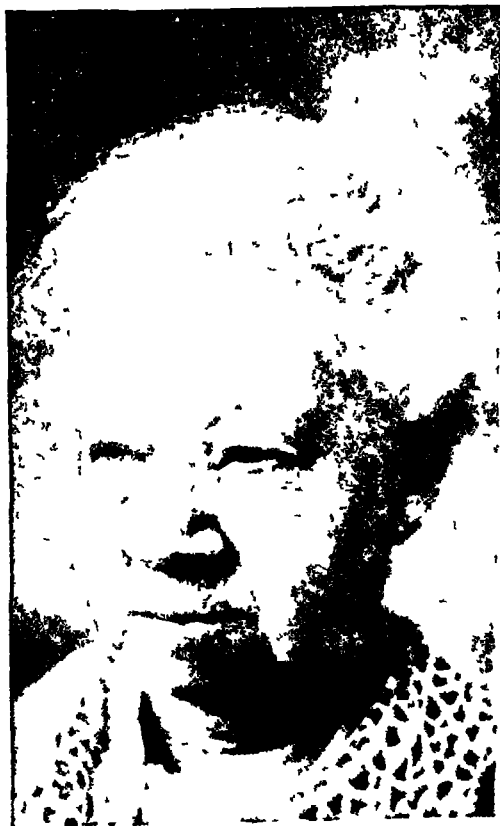


FIG. 5. Case V. A, taken on Feb. 1, 1923, with basal metabolic rate —22, corrected for age; B, taken on April 23, 1923, with basal metabolic rate normal.

metabolic rate was -24 . The rest of the examination was not remarkable. The most important data, as is usual in these cases, were supplied by a member of the family.

The outstanding features, according to her daughter-in-law, were her selfishness, deceit, and extravagance. As she did not like one of her daughters, to eliminate her from the home, she consented to her making an undesirable marriage, notwithstanding the protests of her husband, relatives, and friends. Her son was not able to remain at home because of the "everlasting nagging and bickering." Though faultfinding in her home, she was very boastful of her children when talking to others. She would suddenly decide to visit friends at most unusual and inconvenient times, leaving home without making any provision for someone to take care of the fires or the house. Untruthfulness was also a conspicuous feature. A curious eccentricity was a remarkable fondness exhibited towards her son-in-law notwithstanding the fact that he ill-treated his wife (her daughter). Finally, her husband, his patience utterly exhausted, left her.

Under thyroid administration she made a very satisfactory recovery and during recent years, though over 70, she has worked much of the time as a practical nurse.*

Attention has been drawn by Lund and Benedict² and later by Benedict,³ to the fact that patients with myxedema are unduly susceptible to morphine. They state that not only

does morphine cause a drop in the basal metabolic rate of ten per cent in normal rabbits but that in hypothyroid rabbits the drop is twenty per cent. They report several cases in which alarming results followed the use of morphine in patients with myxedema.

One instance is given in which the condition had been unrecognized for years, the patient received morphine three times for various operations, each time causing grave concern to the surgeon. Another patient who reacted badly to morphine when the metabolic rate was low, subsequently showed no untoward symptoms to the drug when the rate was above normal. One patient died. In this connection the following case is of interest.

Case VI Two years ago, a middle-aged Italian woman was admitted to my service, complaining of dizziness and weakness. She had not been able to work for seven or eight years. She was apathetic, rather obese, with moderate hypertension. Complete laboratory and x-ray investigation was negative except for basal metabolic rate which was -19 .

She showed much improvement after three weeks of thyroid feeding at which time the metabolism index was -11 , later it dropped to -16 . On the day the last test was recorded, she had a molar tooth, about which there was an abscess, extracted under gas-ether anesthesia. She was given one-sixth grain of morphine hypodermically, at 11 45 A. M. During the extraction she stopped breathing, at 1 10 P. M., and was pronounced dead at 1 30. Artificial respiration and intracardiac stimulation proved unavailing. Respiration ceased 85 minutes after the morphine was given. Autopsy was not obtained.

It is of course speculative as to the cause of death but in view of Lund and Benedict's work, it is at least suggestive that the combination of morphine and myxedema played a part.

*This patient died in September, 1932. An autopsy was performed by Dr. W. M. Allen. The microscopical examination of the thyroid showed that about two-thirds of the gland was made up of dense cellular fibrous tissue. There were small islands (2 mm.) of lymphocytic infiltration. In the center of these there remained a few atrophic distorted thyroid follicles. The epithelium was markedly atrophic and an occasional acinus contained a small amount of markedly eosinophilic colloid. There appeared to be no functioning tissue. The heart and liver showed fatty degeneration.

When morphine poisoning occurs in known or suspected myxedema, the intravenous use of thyroxin, as used by Lund and Benedict, is probably the best possible treatment

The anemia that accompanies myxedema may be of the so-called secondary type due to the low level at which the blood-forming system is operating or to blood loss as frequently occurs from bleeding hemorrhoids. Sometimes true pernicious anemia coexists and it is essential to administer both thyroid and liver to obtain complete amelioration of symptoms.

Mason, Hunt and Hurvath⁵ found that with true myxedema there was a marked elevation in blood cholesterol that did not obtain in low metabolic rates, unaccompanied by clinical evidence of myxedema. As the metabolic rate rises, the cholesterol falls and is below normal when the patient is hyperthyroid.

That there is a "myxedema heart" has been asserted and denied. Characteristic findings are described as being⁴ "a heart enlarged in transverse diameter, prolongation of the interval between auricular and ventricular contraction, an inversion of "T" wave in all three leads, small "P" waves and slurring of QRS complex. White" considers a flattening or inversion of the "T" wave in all leads "almost pathognomonic" of myxedema. When cardiac symptoms are present, thyroid should be administered but the initial dose should be small. These patients are often benefited but untoward results may occur.

Lack of perspiration is characteris-

tic of myxedema. Accordingly we were much interested a few years ago in a patient with this disease who perspired profusely on the palms of the hands. They were literally dripping wet.

Save for the occasional patient who is so psychotic that mouth medication cannot be carried out, there does not appear to be any reason for using thyroxin intravenously. The sudden and violent readjustment of the body can be avoided by the use of a potent tablet by mouth. Murray who appears to have been the first to administer thyroid to a patient with myxedema, used a preparation of sheep thyroid and his patient died at the age of 74 years, after taking the treatment for 28 years.

Though patients with spontaneous myxedema require thyroid all their lives, those with myxedema following radiation for toxic goiter often need it for only a few years, due presumably to regeneration of the gland.

Patients with myxedema often spend a great part of their lives and a large amount of money in a vain quest for health as their varied complaints take them in turn to nearly all the specialists in the healing art. Not infrequently they are committed to hospitals for mental diseases. The frequent failure to recognize the condition is particularly deplorable because the transformation of what Osler referred to as "a poor, awkward, toad-like caricature of humanity" into an alert normal person by the administration of thyroid is one of the triumphs of medicine.

REFERENCES

- ¹REPORT OF COMMITTEE ON MYXEDEMA
Trans Clin Soc of London, 1888, Supplement to XXI
- ²LUND, C C, and BENEDICT, E B Influence of thyroid gland on the action of morphine, New England Jr Med, 1929, cci, 345-353
- ³BENEDICT, E B · Morphine in myxedema, Jr Am Med Assoc, 1930, civ, 1916
- ⁴DUDEN, C Myxedema with cardiac decompensation and hypertension which disappeared under thyroid medication, Jr Mo Med Assoc, 1929, xxvi, 25-27 Discussion by David Barr
- ⁵MASON, R L, HUNT, H M, and HURNTHAL, L M Blood cholesterol values in hyperthyroidism and hypothyroidism their significance, New England Jr Med, 1930, cciii, 1273-1278
- ⁶WHITE, P D Heart disease, 1931, The Macmillan Company, New York, 388

The Question of 'Primitive' Syphilis

“THAT the character of syphilis in the indigenous population of Asia and Africa differs in many respects from European syphilis can hardly be denied. In accounting for this marked difference, Bramsen repeats the usual suggestions of ‘spirochetal strains’, varieties of racial and social ‘soil’ ‘lack of treatment’, ‘racial immunities’, and the antisiphilitic action of tropical fevers, notably malaria. Mere mention of each suggestion reveals how little is known, and Bramsen indicates that the Orient offers itself as a laboratory not only on the history and epidemiology of syphilis, but also on its diagnosis, treatment, and control.

“There seems to be in the minds of writers on tropical medicine a concept known as ‘pandemic syphilis’, which, to quote one reviewer ‘is contracted in childhood, the primary lesion passing not unnoticed but unnoted in a lowly living population among whom sores and ulcers are disregarded. Syphilis under such conditions may almost be regarded as one of the exanthems of childhood. Following the marked dermal reaction a considerable degree of immunity results and neuroparenchymatous siphilitic lesions do not develop.’ In the mind of this reviewer this is ‘acquired syphilis as seen in children’, in which ‘none of the well-known stigmata’ of the congenital disease are present. Another pathologist prefers to call this ‘endemic’ syphilis, Butler writes of ‘primitive’ syphilis, and others refer to ‘tropical’ or ‘indigenous’ syphilis.

“There is doubtless general agreement that there exists among the lowly population of huge areas of the world a tremendous amount of treponematous infection, but when one begins to search textbooks and literature for a description of this pandemic syphilis, one finds almost no information as to its clinical character, its serology and immunology, its epidemiology, its proper treatment, and the criteria for its cure.

“Most writers and reviewers of the literature of tropical medicine are taken up with yaws and with its differentiation from syphilis, to the exclusion of the larger subject as to the nature of syphilis itself in primitive peoples. Advocates of the duality of the two diseases overlook the fact that their strongest argument would be to delineate the symptoms and pathology of this pandemic syphilis which they state exists as a distinct disease side by side with yaws in tropical countries.”

(Quoted from FREDERICK H. HUDSON, *Syphilis in the Euphrates Arab*, Am Jr Syph, 1932, xvi, 447-469.)

Historic Montreal: Metropolis of Canada and Mother of the Cities of the West

By MAUDE E. ABBOTT, B A , M D , F R C P (Can),
McGill University, Montreal

FOR the first time in its annals the College is to meet in this beautiful metropolitan city that clusters around the slopes of Mount Royal and extends to east and west below these along the banks of the St. Lawrence as far as eye can reach. Snow-girt she will be then, and sparkling in her winter garment in air tingling with ozone that breathes of those mighty regions beyond of which she is at once the haven and the gate. For Montreal, the second largest seaport on this continent is the only one that lies 1 000 miles above the ocean to which her liners sail. She stands too at the confluence of the Ottawa and the St. Lawrence, those mighty river highways that lead, the one northward to its source, and the other inland by way of the Great Lakes to the heart of the American and Canadian West. It was this location, so favorable for the command of the water-ways as well as the intrepidity of her first *rovaqueurs*, that brought such phenomenal success to the early explorers from Montreal and the vicinity who first penetrated the vast fur-trading regions of this Continent and established outposts of civilization at many far-flung areas that have since become teeming centers of population both in Canada and the United States.

Moreover this great city which now

numbers some 1,200,000 inhabitants, had origin in a spirit of lofty idealism and a splendid fortitude that make its record a living force in world history today. Her foundations were laid amid thrilling scenes of Indian warfare and French heroism by a mere handful of devoted men and women, in whose hearts the zest of discovery and the love of adventure burned with a flame tempered by a profound religious faith to the steady light of a true consecration. Her boundaries extended and her resources multiplied with the years in spite of adverse trade conditions, devastating epidemics, internal dissensions and the many difficulties that marked the passing of the old *regime*. From these vicissitudes she has emerged today the fifth city on this continent in point of population, the commercial metropolis of the Dominion, the seat of twelve large hospitals and of two great Universities representative of that dual culture in which two nations live united under the British flag. For in this Province of Quebec which has rightly been called the nursery of the British Canadian as well as of the French Canadian race and their institutions modern Canada is hunched as well as ancient Canada preserved.

The history of Montreal is that of a

one of merely local interest, but concerns the entire American continent. For Montreal gave de La Salle, Marquette and Joliet to the discovery of the Mississippi, Du Lhut, Radisson, Nicolet and others to the penetration of the middle West, de la Verendrye and his sons to the pathfinding of the Great Lake districts and beyond, Archibald MacDonald and John McLaughlin to the civilization of Oregon, Alexander Henry and David Thompson to British Columbia and the Canadian West, these and many others, including "Bienville, Iberville, Laclede, Cadillac, Mackenzie, and Fraser, whose revered names live in eternal history from Louisiana to the Atlantic Ocean and across the continent to the Pacific Coast. New Orleans and Chicago, St. Louis, Detroit, Fort William, Duluth, St. Paul, look hither for their originators"³ Montreal was the headquarters, too, of Lord Selkirk in his settlement of the Red River District in Manitoba under the Hudson's Bay Company and it was the seat of residence and operation in the early nineteenth century of those pioneers in commerce and education, the great fur magnates of the Northwest Company of whom James McGill was one.

From this colorful record of the pioneer achievements of so many brave men, one turns with no less vivid interest to the city's own past, and to the evolution of its hospitals and medical schools and of those outstanding physicians whose names are linked with each advance. For many generations the main life of the town centered around its religious and philanthropic activities. So that alike in the birth and growth of the early French hospitals and in the foundation of that first

great British-Canadian charity, the Montreal General Hospital, we see reflected the most conservative and representative elements of the community grouped in concerted action for the common weal.

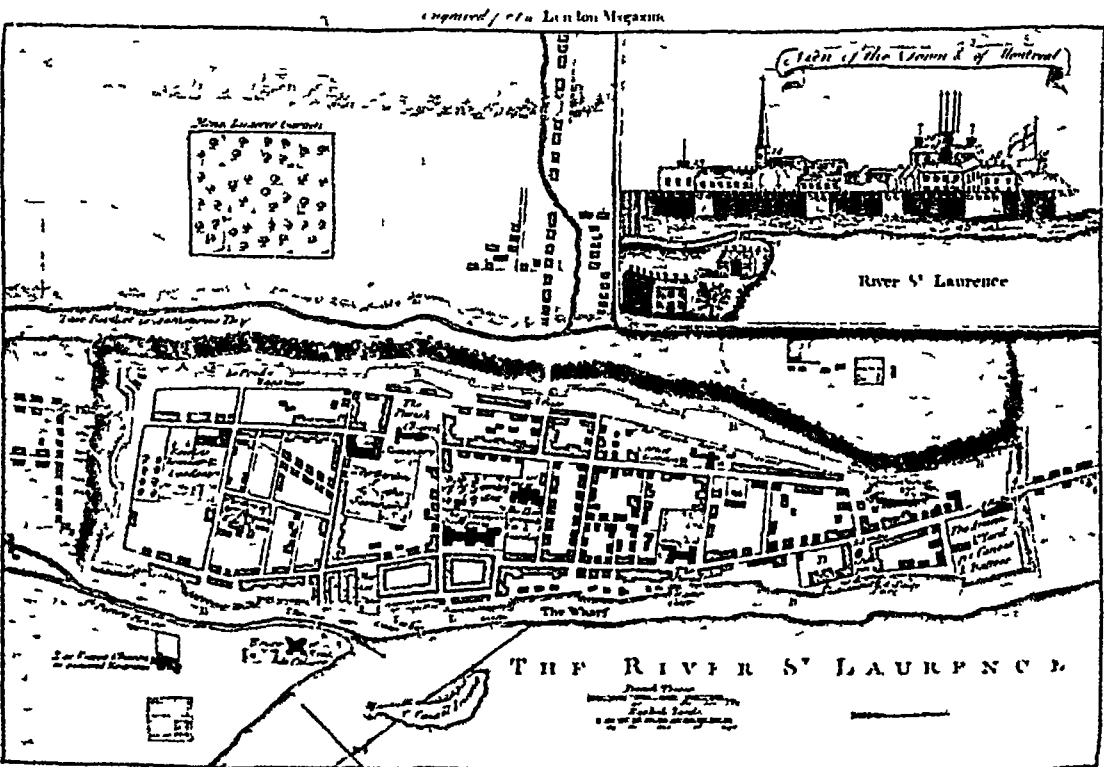
The first hospitals on the American continent were founded in Quebec Province, one the *Hôtel Dieu du Précieux Sang* at Quebec in 1639, and the other, the *Hôtel Dieu de St. Joseph* at Montreal in 1644. Indeed, this latter may be dated earlier, in 1642, with the foundation of Montreal, for Chomedey de Maisonneuve, with Jeanne Mance in his company, landed at the Pointe aux Callières (the present Custom House Square) in May of that year and in the log "habitation" erected by him on this spot and occupied by his little force in March, 1643, a couple of rooms were reserved for her and for the sick, and there was also a dispensary. The first Hotel Dieu building was erected, however, with funds from Mme de Bulhon, on land that is still the property of the nuns of St. Joseph on the corner of St. Paul and St. Sulpice Streets and was opened to patients in October, 1644. It had attached to it a modest farm of four *arpents* with two bulls, three cows and twenty sheep. There was a building 60 by 24 feet with two wards, a kitchen and a serving room, as well as a room for Mlle Mance who had sole charge of the sick until her return from France in 1659, when she brought with her three nuns of St. Joseph, to whom on arrival she made solemn transfer of her beloved hospital. Mlle Mance, however, continued to administer its affairs until her death in 1673. On two occasions she saved the little colony from impending dissolution by going to Paris and securing



FIG. 1 Statue of Jeanne Mance tending a wounded soldier, by Philippe Hubert (1900), photograph from the clay model in the artist's studio, from which the bronze statue was cast in the courtyard of the present Hotel Dieu of Montreal was cast in 1901. (See p. 100)

in 1649, the reorganization of the tottering Société de Montréal, and again in 1651, obtaining there 22,000 livres to assist de Maisonneuve in the transportation of 100 men to hold the colony against the Iroquois. The terrible incursions of these relentless foes and the indomitable resistance presented by its defenders, together with the bitter cold of the Canadian winters in their imperfectly constructed building, make the tale of Jeanne Mance and these first hospital nuns who took over her work, one of almost unprecedented womanly heroism and a dauntless courage and self-devotion that has not often

found its parallel in history (See figure 1) This first hospital was burnt down in 1695, and again in 1721 and 1734, and was rebuilt thereafter as shown in figure 3. Until the English General Hospital was opened in 1822, the Hotel Dieu was the only medical hospital in Montreal, and it functioned as such through the great epidemics prior to that time and assisted in the military exigencies of the wars of 1760, 1765, and 1812. It was removed to its present site in 1861 and since then has had repeated extensions for purposes of modern equipment as shown in figure 13.



Plan of the Town & Fortifications of Montreal or Ville Marie in Canada

FIG. 2. Plan of Montreal in the year 1758. Showing the city surrounded by a wall which was four feet thick and nine feet high. At this time the town lay along the river front entirely below Craig Street which was then the bed of a small river and is seen here running from East to West near the top of the picture. The "old Hotel Dieu", entitled here "The Nursery Hospital", is seen lying on the upper side of St. Paul Street just to the left of the Seminary Gardens and the Parish Church above these. The Hôpital Général or the Freres Church occupies the site of the present Custom House Square, in the left foreground of the picture below the little river St. Peter. (From a print in the possession of the David Ross McCord Museum of McGill University.)

The *Hôpital Général* of Montreal, another venerable institution, was founded in 1694 as a House of Charity by François Charon in a building erected by him for the purpose near the river front at the foot of St Peter Street (see figure 2) After his death it fell into disrepute but was revived, with extended powers for the care of foundlings and the insane, in 1747 by Mme d'Youville, Head of the Order of Grey Nuns It functioned actively in these

distinguished authority on the local history of Montreal, have a mass of well indexed notarial material dating from the arrival of Maisonneuve in 1642, and are well worthy of a visit From these and from Mr Massicotte's publications a few notes are extracted here

The first medical names are those of *Louis Goudcan*, who is said to have accompanied Maisonneuve in 1642, and whose name is attached to the first notarial deed executed by Lambert Closse in 1642 and *Jean Poup-*

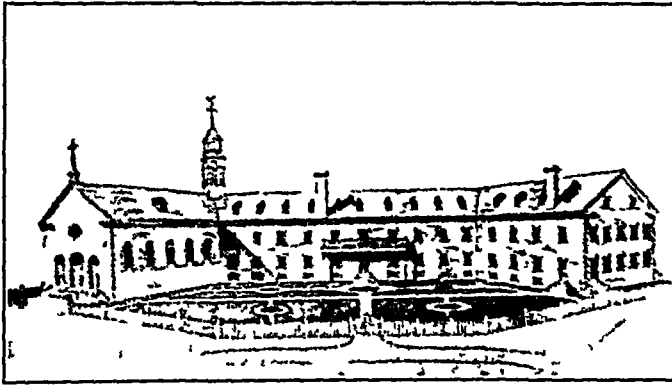


FIG 3 The Old Hotel Dieu Hospital, situated on St Paul Street, between St Sulpice Street and St Dozier Lane Begun in 1644, it was demolished about 1861, when its successor the Hotel Dieu of today was opened on Pine Avenue at the northeast corner of Fletcher's Field

ways and on occasion also as a military hospital until the middle of the nineteenth century, but has now become, under the name of the *Grey Nunnery*, a huge charitable institution for foundlings and the infirm It removed in 1871 to the corner of Guy and Dorchester Streets and is no longer a hospital

MEDICAL PRACTITIONERS IN MONTREAL DURING THE SEVENTEENTH AND EIGHTEENTH CENTURIES

The Archives of the District of Montreal housed at the City Hall under the care of Mr E Z Massicotte,⁴ the

pec who officiated at the entrance into the world of the first children of European parentage born at Ville Marie These men must have helped Jeanne Mance at her infant hospital but the first name officially attached to the Hotel Dieu is that of the *Abbe Sarrat*, first Sulpician cure of Montreal who had learned Medicine in earlier years and attended there from his arrival in 1657 to 1659 He was succeeded by *Etienne Beuchard*, a master-surgeon of Paris and a man of parts, who arrived in 1655 in the service of the Company of Montreal under an engagement for five years in return for an advance payment of 147 livres, he held the appointment of surgeon to the Hotel Dieu from 1659 to 1702 by a quaint deed of death he was supplied with medicines two years before he died in Montreal for twenty years before he died

per person so treated *Louis Chartier* also came out in 1653 in the service of the Company and was the friend and financial supporter of *Dollard des Ormeaux* but was himself drowned in the Ottawa in 1660 while defending the upper end of Montreal Island against the Iroquois

Bouchard was succeeded on the Hotel Dieu from 1674 to 1680 by *Jean Gaillard* and the latter by the two surgeons and medicolegal experts, *Jean Martinet* and *Antoine Forestier*, who were officially appointed in 1681 in

1681 *me Guestin*, midwife for the community. *Daniel Debonne*, who had taken medical degrees abroad, was physician to the Hotel Dieu of Montreal from 1770 to 1780

EARLY LICENTIATES UNDER THE ACT OF 1788

A very important French Canadian physician practising in Montreal in the years just succeeding the conquest was *Jean Bte Jobert* who took an active



FIG 4 Chateau de Ramezay on Notre Dame Street, once the residence of the French and Early English Governors Built in 1705, and now the Museum of the Montreal Antiquarian and Numismatic Society

an interesting deed which pledged them to "dress and treat the patients" in alternate quarters and to visit them diligently at 7 o'clock every morning and at other times when necessary at request "for 75 livres a year each, the remedies being supplied by the hospital". An important physician in Montreal in the next generation was *Dr Joseph Benoit*, surgeon and *medecin du roi*, who was on the staff of the Hotel Dieu from 1715 to 1719. Associated on it with him for a few years was the Irishman, *Timothée Sylvestre*, who obtained his license, under an order from the King, from the famous *Dr Michel Sarrazin* of Quebec by personal examination. A curious deed of this time reveals that the women of Ville Marie in solemn convocation assembled on Feb. 12, 1713 elected Cotte-

part in the campaign then going on against the Baie St Paul disease, the malady, apparently an obscure epidemic form of syphilis, that was then ravaging the country from the Lower St Lawrence to the Upper Ottawa. His name is attached to a license dated 1788, granted by the first Licensing Board of the District of Montreal to *Henry Loedel*, father of H. P. Loedel, a member in the next generation of the first Medical Board of the Montreal General Hospital. With it are affixed the signatures of *Xavier Bender*, *Charles Blake*, *Robert Sym* and

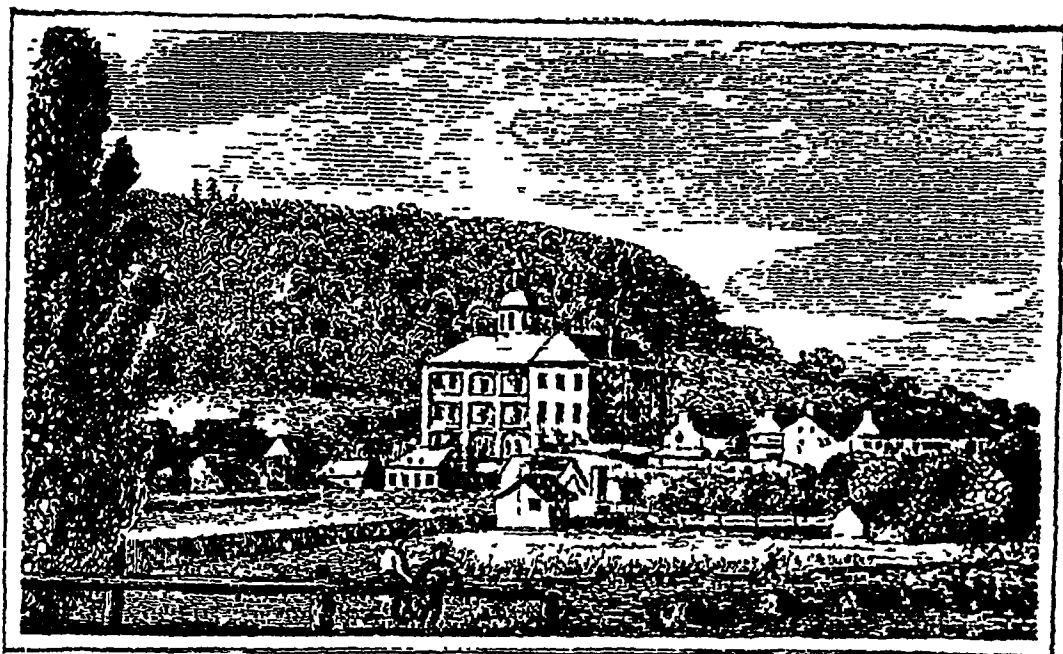


FIG 5 The Montreal General Hospital in 1831, as seen from the rear, showing the central building erected in 1822 and the Richardson wing, before other additions had been made. From *Hochelaga Depicta*, 1839.

George Selby, a galaxy of well qualified physicians who practised medicine in Montreal in the latter part of the 18th century and who did yeoman work in the struggle for securing the medical legislation against quackery that resulted in the first Licensing Act of 1788. Dr Loedel entered later into partnership in Montreal with Dr Blake, who was a retired army surgeon and evidently a man of substance, for another interesting deed, dated 1785, records the sale to him by Elijah Cady of Boston, of three negroes "Tobi, Sarah and Boye" who remained in his possession a long time as attested by a notarial endorsement upon it thirteen years later.

An examination of early licenses in the Dominion Archives at Ottawa reveals many interesting facts. The first French-Canadian doctor to study abroad appears to have been Jacques Labrie, who took an Edinburgh degree

in 1807 and was granted the Provincial license for the District of Montreal in 1808. He wrote a history of Canada and practised at St Eustache some 25 miles from the city. On June 18 1795 a license bearing the signatures of Charles Blake, Robert Sym and John Rowand was granted to the famous Daniel Arnold called later the *Doyen* of the profession in Montreal who was long a member of the Board of Examiners, became the first President of the College of Physicians in 1841 and died in 1849.

Under the conditions engendered by the Act and from other causes the dawn of the nineteenth century saw a better class of physicians appearing in the Province. A new generation had arisen of Canadian (or in a number of cases American) born practitioners who after receiving their professional training through a local apprenticeship proceeded to qualify for the Province.

cial Licentiate either by passing an examination before one of its District Boards or by obtaining a degree or diploma abroad. To these were added a few highly qualified British surgeons who had settled in the country after the war of 1812 and who played an important part in elevating professional standards and in formulating that demand for higher medical education that had already found expression in the organization of courses for medical students both at Quebec and Montreal as much as twenty years before the ultimate successful formation of the Montreal Medical Institution in 1823.

Thus it came about, that, in the second and third decades of the century, we find on the list of Licentiates for the District of Montreal a group of highly significant names, of men who, by their subsequent labors, set in motion an educational force that extended far beyond their own day and place. For these men, who became later the Founders of the future Medical Faculty of McGill, brought with them from their own school at Edinburgh, of which they were all four graduates, that precious gospel derived from Leyden, of clinical teaching at the bedside that is the keystone of the best medical education today. So firmly did they implant this doctrine in the principles of their infant institution and in the hospital from which it sprang, that it became for the successive generations of teachers here a living force. To it McGill's greatest graduate, Sir William Osler, owed and acknowledged his inspiration and he transmitted that early influence throughout this continent in his later years.

First on the list for the District of Montreal for the year 1816, stands the

revered name of *Andrew F. Holmes*, who later became the first Dean of the McGill Medical School. At that time he was a youth of 24, fresh from a classical education at Dr. Skakel's school and five years' apprenticeship under Dr. Arnold. Along with *John Stephenson*, his life-long friend and later co-worker on the McGill Faculty, he proceeded to London, Paris and Edinburgh where he graduated M.D. in 1819. Stephenson took a London degree in 1819 and one at Edinburgh in 1820, returning to receive the Provincial License in 1821, he became and remained for many years the Secretary of the Montreal General Hospital and Registrar of the McGill Faculty and has been universally acknowledged as "the man of all others who saved the bequest of James McGill to his University." In 1817 *Dr. William Caldwell*, a surgeon of the 34th Regiment of Dragoons, obtained his license, and *William Robertson*, a surgeon of the 59th Regiment, retired after the War of 1812, who was the fourth founder of the McGill School and long a member of the Board of Examiners for the District, fulfilled the necessary formalities in 1828. Another distinguished licentiate of the year 1828 was *Dr. Pierre Beaubien*, who graduated from the University of Paris in 1822, and after practising in that city for several years returned to Montreal to follow a career of great influence, especially upon medical education in the French-Canadian Schools. He is said to have introduced the use of the stethoscope into Canada. For many years he was a Professor in the *École de Médecine* of Montreal and later he became Dean of the Laval-in-Montreal Medical School and member for Mont-



FIG. 6. Montreal in 1952. View from Mount Royal, showing the Arts building and Bursar's Office of McGill College in the foreground, and the city proper below. The city proper lay below St. Catherine Street, and Sherbrooke and University Streets are visible. The Montreal General Hospital with cupola and Richardson and Reid wings is seen in the left center and near the river-front is the old Hotel Dieu. (From the Whitfield Print in the possession of the David Ross McCord Museum at McGill University.)

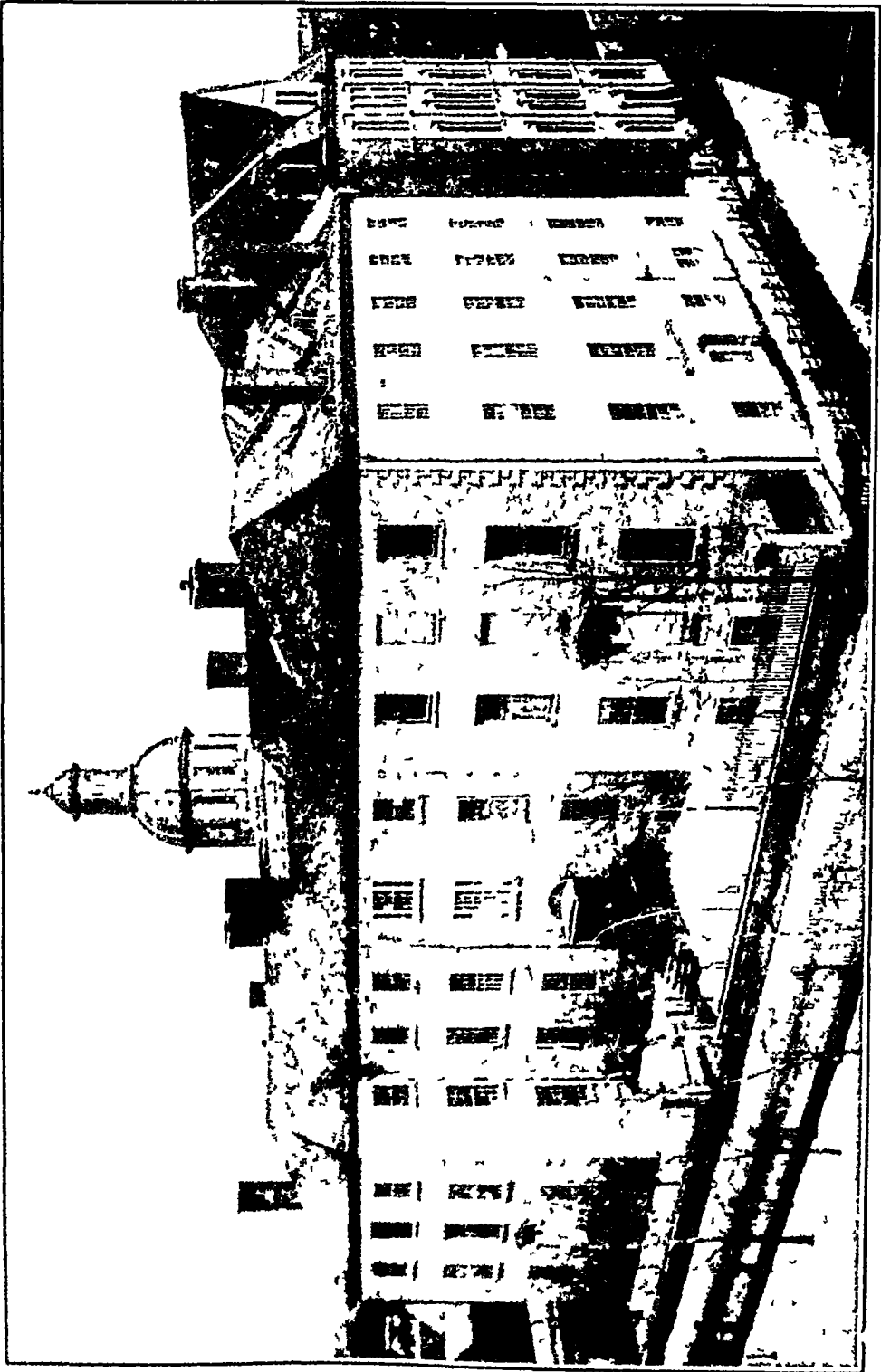


FIG 7 The Montreal General Hospital in 1881 as it was at the time of Osler's service there, showing the central block with its cupola and sloping roof, as erected in 1822, and the Richardson and Reid wings, erected in 1831 and 1848, on either side, and the Thomas Morland wing behind

real in the Legislative Assembly. He left an illustrious name and founded an important family.

ORIGIN OF THE MONTREAL GENERAL HOSPITAL

This important development, which marks an epoch in the history of medicine in Canada, took form as a direct

stranded within her precincts. Failure of the crops during the summer of 1816 intensified the distress by impending famine, and in addition the lack of accommodation for the care of the sick poor made itself desperately felt, the Hotel Dieu being at that time the only hospital and provided with only thirty beds. In the winter of 1817 public



FIG 8 Osler in 1871, when a student at McGill University, from which he graduated in 1872

result of the distress of the poorer population in Montreal in the years immediately succeeding the battle of Waterloo. With the cessation of the European war there came a great influx of immigrants into Canada and this thriving little town then of some 16 000 inhabitants was overwhelmed by the flood of indigent and debilitated persons arrived from overseas whom the onset of the winter season left

legislation was enacted and private philanthropy engaged to meet this appalling crisis. It is an interesting historical fact that Montreal's first great civic charity, the English General Hospital, originated at this time through the initiative and activities of a small group of influential women who organized themselves for the relief of the "Distress of the Lower Class of the People" and "to alleviate those who

ful sufferings" of the indigent poor, under the name of the *Female Benevolent Society*

Two years later in the autumn of 1818, this Society succeeded in establishing a soup-kitchen to which was attached a small house of four rooms for the care of the sick called the "House of Recovery", situated on what is now Chaboillez Square. So successful was the work carried on there during the first twelve months of its operation that it was handed over to a group of business men and a larger house capable of accommodating twenty-four patients with three wards situated on Craig Street was leased and thrown open to patients on May 1, 1819, with "four professional gentlemen"* in attendance, one of whom (Dr John Stephenson) acted as house-surgeon. To this house the name Montreal General Hospital was given and here regula-

*Drs Holmes, Stephenson, Caldwell and Robertson

tions were framed, Quarterly Reports issued, and work carried on until May 1, 1822, when the present Montreal General Hospital on Dorchester Street was opened, the building at that time consisting only of the original central block surmounted by a cupola and protected in front by the iron railing that is still in place (see figure 5). This building had been erected at a cost of £5,856 of which amount a little over £2,100 was subscribed by the public spirited citizens of Montreal and the balance paid in the following year by the Hon John Richardson. Three other wings were added in the succeeding decades, in 1831, 1848 and 1874, and a smallpox building (since taken down) was erected within the enclosure in 1868, of which Dr Osler was put in charge in 1875 and himself became a patient there with this disease. It was on the basis of this experience that he wrote his "Initial Rashes of Smallpox". In 1874, also, he was appointed

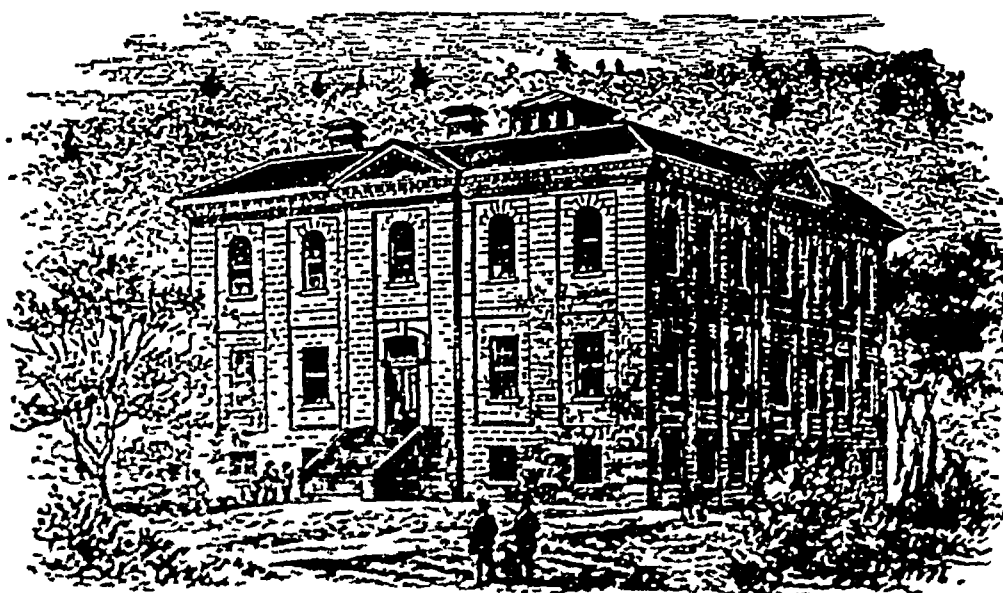


FIG. 9. The first building of the McGill Medical Faculty in the university grounds, in which Osler lectured a professor of the Institutes of Medicine from 1874 to 1884. Erected in 1872 and destroyed, with its extensions, by fire in 1907.

Pathologist to the Hospital, there inaugurated the first systematic autopsy service in Canada, and performed during the ten years of his service 750 autopsies, thereby gaining most of the rich experience embodied in his Practice of Medicine. Some 150 specimens collected by him at these postmortems

actual headquarters of a medical school and for the instruction of students, who were to be admitted, following the example of Edinburgh, freely to the wards for clinical teaching and study. That this was understood as far back as 1819, is evident from the words of Dr. Charles Perrault of Quebec, speaking



FIG 10 The Central Medical Building of McGill University erected in 1910, and now in occupation. It contains Administration offices, Medical and Osler Libraries, Anatomical Medical, and History of Medicine Museums, and Departments of Anatomy, Histology and Public Health.

are preserved in the Historical Medical Museum at McGill and are interesting as the basis of many of his early publications.

RISE OF THE MONTREAL INSTITUTION AND THE MEDICAL FACULTY OF MCGILL UNIVERSITY⁶

From the first organization of the English General Hospital in 1819 it was clearly formulated, thanks to the insistence of its first Medical Board, Drs. Holmes, Stephenson, Robertson and Caldwell, and later H. P. Loedel, that the hospital was to be used as the

in the House of Assembly in support of Mr. Molson's motion "for the establishment of a public hospital at Montreal." He said, "Independent of the good which must result from the establishment of a well regulated Hospital to humanity at large another no less important object is obtained by establishing in such an institution a school for teaching the healing art in all its branches."

On October 20, 1822, Drs. Stephenson and Holmes were deputed by the Medical Board to "draw up the regulations that seemed to a committee of

an endeavor at this Hospital" These considerations are couched in historic terms and read "The Medical Officers of the Montreal General Hospital, having seen the great difficulties which the student of medicine in this country has to encounter before he acquires a competent knowledge of his profession,

and considering that the Montreal General Hospital affords the student a facility of acquiring a practical knowledge of Physic never before enjoyed in these Provinces, . have met to consider of the possibility of founding such an institution in this city

They are further encouraged to attempt the formation of a medical seminary when they reflect that the medical school of Edinburgh, the basis of which they would adopt for the present institution, now justly considered the

first in Europe, is of comparatively recent formation—and the early history of the Royal Infirmary of Edinburgh is not dissimilar to that of the Montreal General Hospital" A week later (Nov 27, 1822) a copy of this memorandum signed by all five members of the Medical Board of the Hospital was forwarded to the then Governor General, Lord Dalhousie, with the suggestion that in order to give the new Institution status the Board of Medical Examiners should be reconstituted and made to consist of the Medical Officers of the Montreal General Hospital Lord Dalhousie, whose enlightened attitude on educational matters was well known, expressed his complete approval and sympathy and on Feb 22, 1823, a Commission was duly appointed consisting of the five Medical Officers of

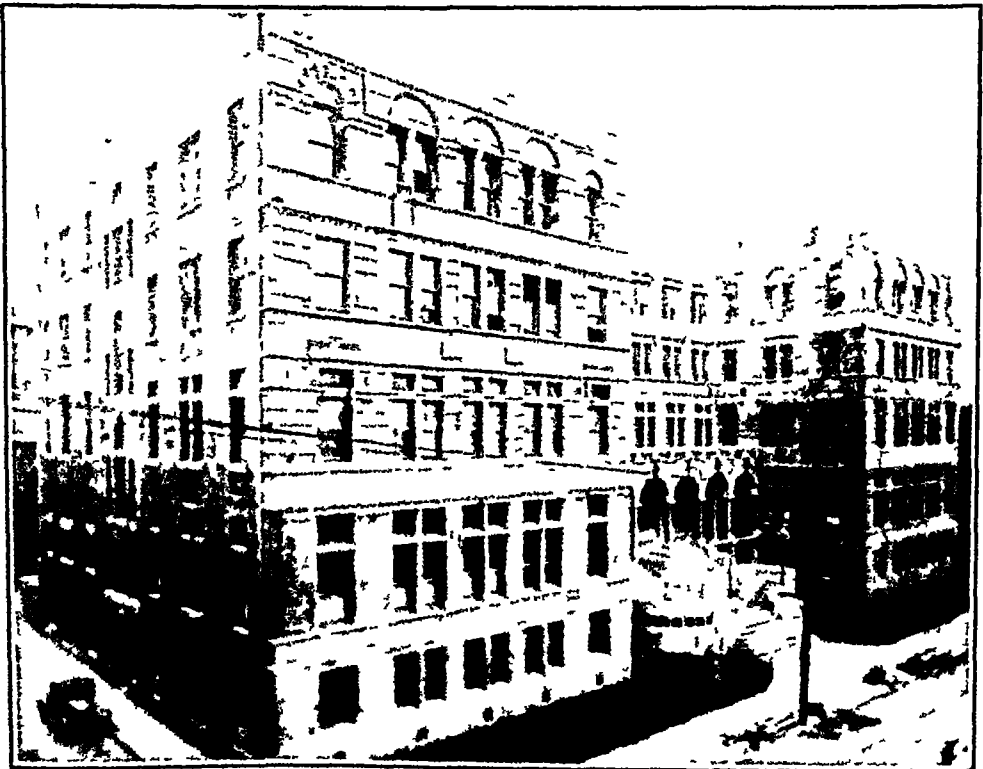


Fig. 11. The Université de Montréal Medical School on St. Denis Street, which is about to be replaced by a large University and Hospital unit now under construction on the western slope of Mount Royal.

the Hospital "any three or more of you" to be the sole Medical Examiners for this District

Delay in the progress of this young Montreal Medical Institution arose from the fact that it was found impossible to obtain a charter for it under which it might be empowered to confer degrees, on the ground that it was not attached to any "Seminary of Learning" nor had it an endowment or foundation. At this time, however, the young University of James McGill which had been established by Royal Charter in 1821 in accordance with the will of the founder, existed only on paper and it had become necessary to institute active educational work in order to retain his

bequest. For both undertakings the psychological moment had arrived, and on June 29, 1829, at the first Governor's Meeting of "Burnside University of McGill College", the memorable step was taken, which gave the Medical Institution its necessary charter and foundation, and McGill an active and highly qualified medical faculty. At this meeting which took place at Burnside House by "Resolution of the Governors of the Corporation" (see figure 6) the members of the Montreal Medical Institution were "engrafted upon the College as its Medical Faculty". The first University degree was conferred in Medicine on Dr W. Logie, May 24, 1833. Throughout its early years this



FIG. 12. Notre Dame Hospital on Sherbrooke Street. Last photograph taken on present site in 1924. Extended and enlarged to its present capacity in 1925. Photograph by permission of Associated Screen News, Montreal.



Fig. 13. The Hôtel Dieu de St Joseph as it is today. The original building as occupied in 1861 is seen in the foreground surmounted by a central dome with massive stone wings on either side. Modern additions shown in the picture are for administration, x-ray department, private wards, and operating rooms (in rear of central dome of old building), pathological laboratory, nurses' home and training school. (An aerial view taken by Cie Aerienne Franco-Canadienne.)

Faculty maintained a relatively high standard for that time, but its most brilliant period may be said to have come in the latter third of the nineteenth century when "attracted by the clinical advantages of McGill", William Osler enrolled as a student and graduated from its portals in 1872. In the ten years of his professoriate there he formed one of a productive group of clinical observers among whom the names of Ross, Howard, Shepherd and others will go down to posterity.

The first lectures of the McGill Medical Faculty were given in a small building on Place d'Armes and later on St. Georges Street in the heart of the city. Later, in 1845, this Faculty occupied the newly-erected Arts Building of McGill University (see figure 6) and remained there until 1851 when it removed to a building on Côté Street near the Montreal General Hospital where it remained until 1872, the year of Osler's graduation. In the autumn of that year it returned to the University grounds, for the first time, to a home of its own (see figure 9) a square building which occupied the site of the present Biological Building and which was unfortunately destroyed by fire, with extensive additions made in 1885 and 1901, in the year 1907. In 1910-11, its present handsome Administration Building with accommodation for Libraries and Museum was erected at a cost of \$600,000 (see figure 10). In it is also housed the Osler Library containing the famous collection of early and historical books of medicine and science made by the late Sir William Osler and bequeathed by him to his Alma Mater. A Biological Building was erected in 1922 and a fine Pathological Institute in 1923 at a

combined cost of \$1,000,000. The latest addition is the fine new *Neurological Institute* under the care of Dr. Wilder Penfield which is being erected near the Pathological Institute at a cost for building and endowment of some \$2,000,000.

THE MEDICAL FACULTY OF THE UNIVERSITÉ DE MONTRÉAL

This is the outcome of an earlier school the story of which is so full of stormy vicissitudes that it reads like a romance. It has been well told by the late Dr. L. D. Mignault,⁵ long a member of its staff. The *École de Médecine et de Chirurgie*, its parent institution, originated in 1843 with the double object of meeting the needs of the French-Canadian student body and in protest against the monopoly of teaching privileges at the Montreal General Hospital by the members of the McGill Faculty. It was founded by Francis T. Arnoldi, Francis Badgley, Pierre Monro and others. It labored under the same difficulty as did the Montreal Medical Institution in that it could not confer a university degree without such affiliation, and licenses to practice were only granted by the Province to persons holding such. After repeated efforts at various affiliations it was united with the "*Succursale de Laval*" as the Medical Faculty of the Université de Montréal with the combined clinical facilities of the Hôtel Dieu, Notre Dame, St. Paul, Catholic Maternity, St. Justine and other French hospitals at its disposal. Since then this Faculty has adopted a very progressive course in accordance with modern standards. Its curriculum reviewed its course of study, approved a pre-medical year, multiplied its clinical

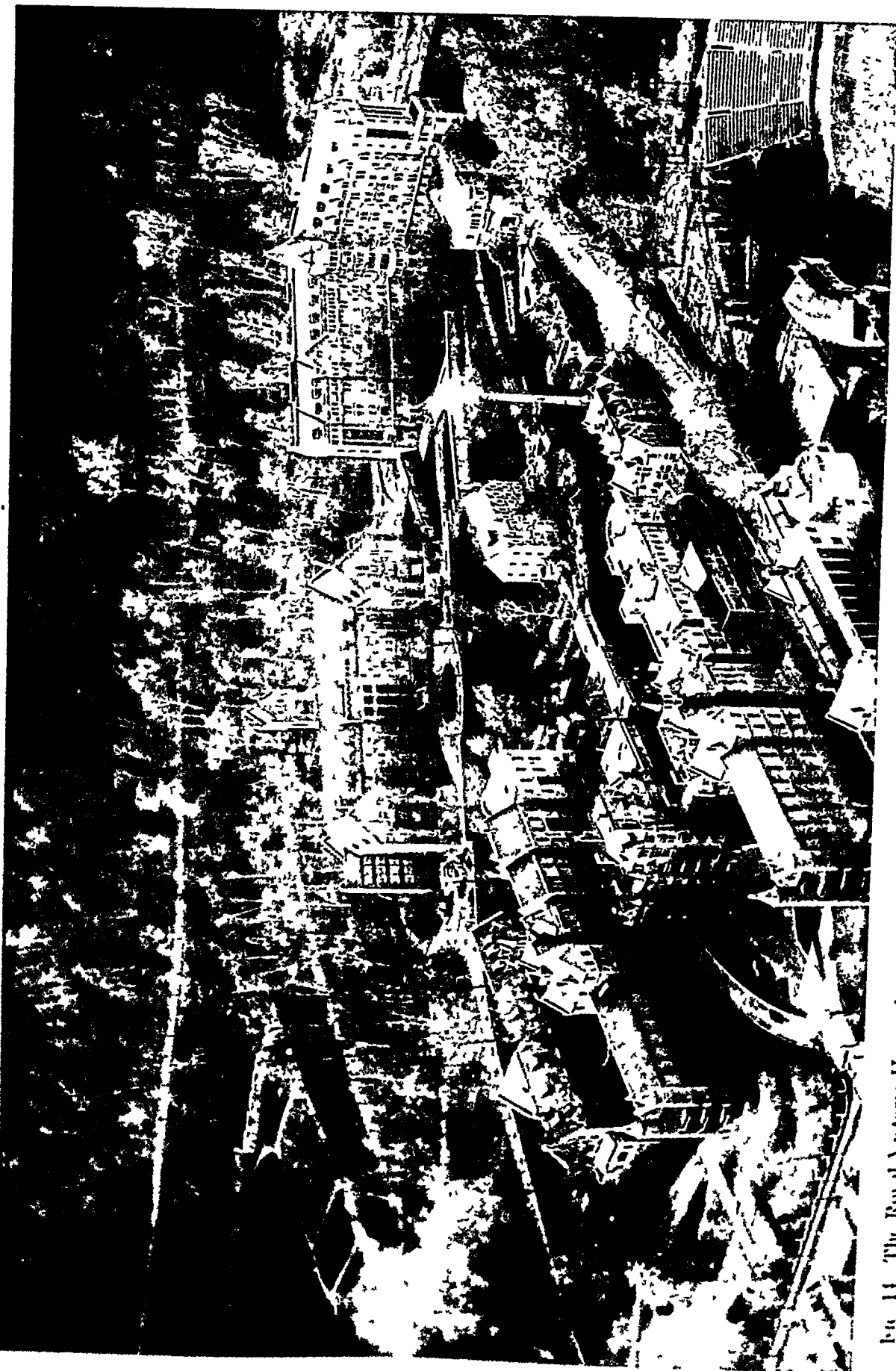


Fig. 14 The Royal Victoria Hospital erected in 1894, showing Administration-block in center with Public Wards on either side, with later additions. Pathological Institute on right with Nurses' Home to the left in the foreground, the Ross Memorial Pavilion for private patients, on the left and the Women's Pavilion (Montreal Maternity Hospital) on the right behind and above the other buildings (From an aerial view, taken in 1920.)

atories while placing these in charge of such men of distinction and international reputation as Prof Pierre Masson, of Strasburg, and improved and enlarged its clinical facilities. Nor is the University of Montreal resting there. A great new building is in process of erection on the northwestern slope of Mount Royal with ample accommodation for all its faculties, including those of Medicine and Dentistry and for a large University Hos-

and a well-equipped x-ray department (under the charge of Dr. Leo Pariseau of medical history fame), and additions made in 1916, 1923 and 1925 are utilized for operating rooms, hydrotherapy, laboratories, Nurses' Home and other purposes. The Hospital is still under the charge of the Hospitalières of St Joseph but a Nurses' Training School was inaugurated in 1901 and underwent affiliation with the University of Montreal in 1920.

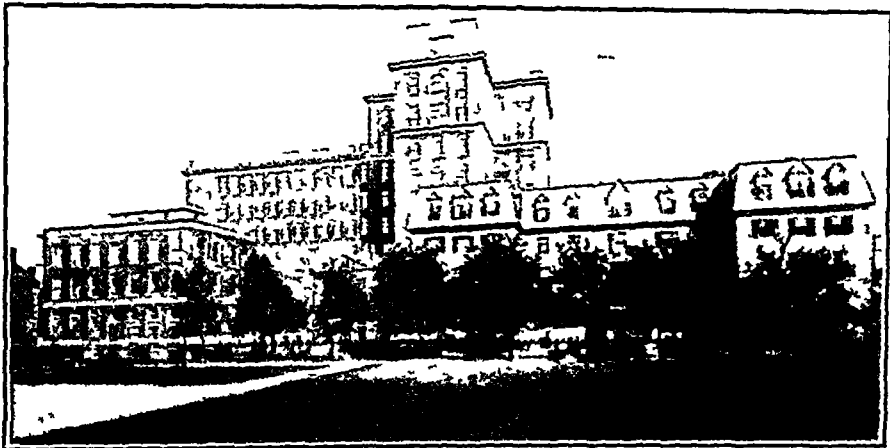


FIG 15 The Montreal General Hospital on Dorchester Street, as it looks today. The old building with its Richardson and Reid wings is surmounted by a mansard roof and on the left are the important new buildings erected in 1913, with, in front of these the Pathological Institute rebuilt in 1909, and completed with extensions in 1919.

pital at a minimum cost of \$3,000,000. Until this building is occupied its Medical Faculty remains on St Denis Street (see figure 11).

HOSPITALS OF MONTREAL TODAY

The old *Hotel Dieu*, removed from that first site on St Paul Street to its ample property on Pine Avenue carries on now in a huge pile of buildings (see figure 13) which includes the original building with cupola of 1861 modernized and brought up to date by many important extensions. A large wing now houses the private wards

The *Montreal General Hospital* still occupies its historic central block on Dorchester Street erected in 1822 (figure 7) with its early additions, the Richardson and Reid Wings but these have been repeatedly altered and it has been enlarged by new additions to its present capacity. In 1882 two new surgical wings, the Greenhalgh and Campbell Wings, were erected and soon after a new and fully equipped operating room was constructed. In 1894 the old buildings were removed and four new medical wards built. An x-ray department was added in 1901

and a pathological building was erected under the charge of Dr Wyatt Johnston, and completed on a larger scale to house Metabolism in 1919. In 1913 the huge new building which towers above at the rear of the original building (see figure 15) was opened and supplies the additional accommodation needed for what is now an up-to-date 400 bed

and progressive French-Canadian institution of 600 beds, which includes 130 beds at present used for contagious diseases, (replacing the old Hôpital St Paul). It was founded in 1880 to meet the needs of the east end of the city and also to supply clinical facilities for the Laval Medical School, now the University of Montreal. Like the

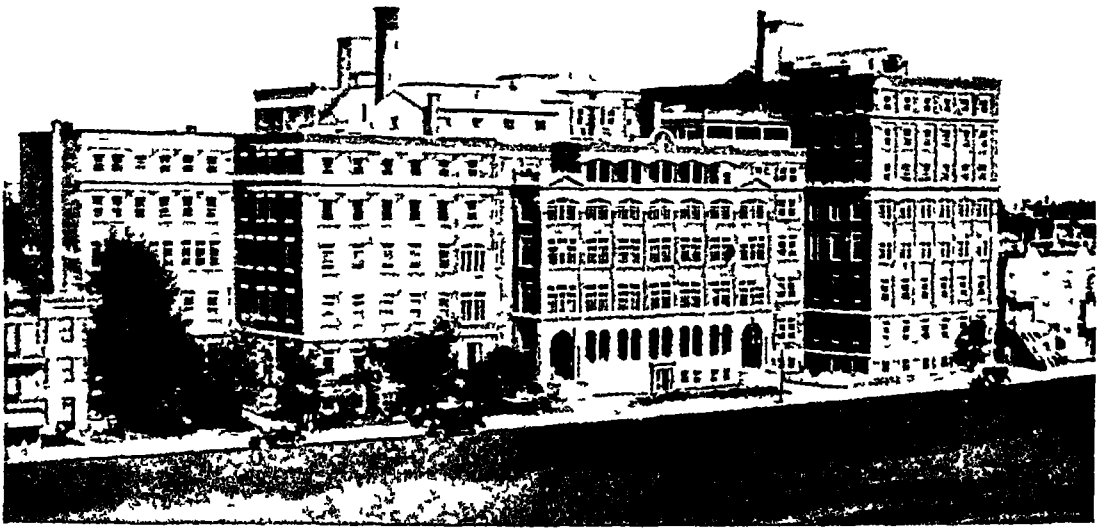


FIG 16 Hôpital St Justine on St Denis Street. Founded in 1907 for sick children under 14 years of age, showing large recent additions.

hospital 'The Nurses' Training School established by Miss *Nora Livingston* in 1890 soon became famous throughout the continent for its high standard and pioneer work. In 1897 a Jubilee Nurses' Home was built and this was replaced in 1926 by a large separate building erected on land opposite the Hospital at a cost of \$600,000.

In 1914 an amalgamation took place of the General with the Western General Hospital which now bears the title of the *Western Division of the Montreal General Hospital*.

The *Notre Dame Hospital* is a large

Montreal General it has been from its inception a public charity, drawing its financial support from the people. The moving spirit in its organization was the late *Dr E. P. Lachapelle* a man of singular force of character and high scientific standards. Originally situated on Notre Dame Street it was removed in 1924 to its present site on Sherbrooke Street opposite Lafontaine Park and has recently been remodelled to its present capacity (see figure 12). A beautiful and commodious Nurses' Home has been erected and was opened in March, 1932. The report for 1931

for this hospital shows that it had nearly 9,000 admissions and 120,000 consultations in that year

The *Royal Victoria Hospital* received its first patient in January, 1894. This beautiful hospital is erected on a commanding site on the side of Mount Royal on a scale commensurate with the new responsibilities and opportunities for the relief and prevention of disease at the present time, and was made possible by the initial gift of \$1,000,000

356 outdoor consultations in the current year (See figure 14)

Another general hospital that is rapidly assuming a major place in the care and prevention of disease in this city is the *Hôpital St Luc*, situated on St Denis and Dorchester Streets. This started in 1913 as an eye and ear dispensary and developed later as an important industrial and dental clinic. Since receiving Federal aid for the care of sailors, it has now 400 beds and a



FIG 17 The Children's Memorial Hospital on Cedar Avenue, founded by the late Dr A Mackenzie Forbes in 1902 with special reference to orthopedic work showing building erected in 1908, with large new wing on the right opened in 1931

from the late Lord Strathcona and Lord Mount Stephen in Queen Victoria's Jubilee Year, and by generous subscriptions from these and other sources since. In 1916 there was added the *Ross Memorial Pavilion*, a complete private hospital of 120 beds and in 1926 a great new *Women's Pavilion* was erected to house the old *Montreal Maternity Hospital* (removed from St Urban Street). The total capacity of this hospital with the above additions is now 700 beds, it being the largest in the Province and its last report shows 14,307 indoor patients and 78

new wing is being added which will bring its capacity to 600. In 1933 it will also open a section for contagious diseases containing 300 beds.

Other important hospitals are the *Hôpital St Justine* 340 beds (founded 1907), (see figure 16), the *Children's Memorial Hospital* on Cedar Avenue 200 beds (founded 1902) (see figure 17) and also the *Shriners' Hospital* (founded 1922), for the care of sick or crippled children, the *Alexandria Hospital* for contagious diseases 165 beds (founded in 1900) and the *Hôpital St Louis*



FIG. 18 Montreal today. Panoramic view from Mount Royal. Shows the river-front with new Harbor Bridge to the left, art on elevators and steamship sheds in center and Victoria Bridge to the right. In the foreground are seen the McGill University Grounds and some of its College buildings, the cupola of the Arts Building with Engineering and Chemistry Buildings in the center and Biological Building above and to the left.

Hospital on Tupper Street, 225 beds (founded 1927)

MONTREAL TODAY

After the above somewhat kaleidoscopic retrospect of the evolution of medicine in early Montreal, only a word can be said regarding what this stately city has to offer to the passing traveller at the present time (Figure 18) Vast changes have supervened since that summer, not quite 300 years

Square and the marble slabs placed by the Historical Society on many buildings in the lower city to indicate the sites of stirring past events in the one time little riverside town Growth and expansion have been very rapid in the past century and especially so in the last thirty years, since when the picturesque river front has been entirely transformed by the gigantic structures of the Montreal Harbor, which stretches from Victoria Bridge (erected



FIG 19 The two remaining towers of the old "Fort des Messieurs", in the grounds of the Seminary on Sherbrooke Street West, built in 1694

ago, when Maisonneuve landed at what is now the harbor front and planted his cross on the western slope of Mount Royal, where later the Sulpicians built their Mountain Fort, the towers of which still stand (see figure 19) Signs of those early days are to be seen in the memorial stone at the corner of McTavish and Sherbrooke Streets that marks the location in Jacques Cartier's day of the Indian village of Hochelaga and in the shining cross on the Mountain top erected by the St. Jean Baptiste Society as also in the Maisonneuve monument on old Place d'Armes

1860) almost to the lower end of the island Montreal is now said to be the largest grain exporting city anywhere and many enormous grain elevators (one the largest in the world), a huge cold storage plant surrounded by twenty-five steel sheds and by miles of grain-carrying belts extend along the shore, for the loading of shipping to all the earth

The river is now spanned by three bridges that of the Canadian Pacific Railway being with Victoria Bridge at the west while the new St. Lawrence Harbor Bridge connects the city to

part of the city to the outlying farm country, Richelieu and Lake Champlain Districts to the South. This bridge, which is $2\frac{1}{8}$ miles long and the largest in Canada and one of the great bridges of the world, is of modern steel construction, costing over \$12,000,000, and was opened on May 24, 1930. At its farther end is the air-port of St. Hubert from which since 1928 Montreal has had an international air service and regular air connection with the United States, the Lower St. Lawrence and Upper Ottawa.

The commercial section of Montreal has at last entered upon the skyscraper

period in the imposing erections of the Royal Bank of Canada (1928), the Bell Telephone Co. (1930), and the Sun Life Insurance Co. (1931). In its amazing growth and expansion of the last few years the city has come to entirely encircle the Mountain which less than fifty years ago formed only its northern background. So also Sherbrooke Street West, long its residential quarter (on which its beautiful Art Association building with its great collection stands), is rapidly becoming commercialized, and the better class houses are being built today on the western slope of the city's greatest asset, her beautiful Mount Royal.

REFERENCES

¹ABBOTT, MAUDE E. "Medicine and Surgery in the Province of Quebec" In "The Storied Province of Quebec" Edited by William Wood, 1931, II, 1066-1150. Also History of Medicine in the Province of Quebec, 1931, 120 pages, 42 illustrations. Published from The Medical Museum of McGill University, Montreal, Canada.

²ATHERTON, W. H. Metropolitan Montreal. In "The Storied Province of Quebec", Edited by William Wood, 1931, I, 605-622, II, 623-781.

³LIGHTHILL, W. D. Montreal after 250 Years. Also, Canad. Antiq. and Numismatic Soc., 1910, III, 192.

⁴MASSICOTTI, F. Z. Les Premiers Chirurgiens de l'Hôtel Dieu de Montreal. Bul-

letin des Recherches historiques, 1924, p. 400, Also, Les Chirurgiens, Médecins, etc. etc. de Montréal sous le Régime Français. Archives de Québec, 1922-23, 131-155, Also 3ième Rapport de l'Archiviste, 1923-24, 163-192.

⁵MIGNAULT, L. D. Histoire de l'Ecole de Médecine et de Chirurgie de Montreal. L'Union Médicale du Canada, 1926, IV, 598.

⁶ABBOTT, MAUDE E. An Historical Sketch of the Medical Faculty of McGill University and of the Origin of the School. With Appendix Montreal Medical Journal, 1902, XXXI, 561-675. Also, Gazette Printing Co., 1902, 114 pages, 30 illustrations.

Editorials

THE JOHN PHILLIPS MEMORIAL PRIZE

At a meeting of the Board of Regents of the American College of Physicians on November 13, 1932 it was resolved that the John Phillips Memorial Prize for 1933 be awarded to Dr WILLIAM B CASTLE, of Boston, for his series of studies showing the relation of gastric digestion to the pathogenesis of anemia, proving the rôle of extrinsic and intrinsic factors in hematopoiesis, and finally demonstrating that the extrinsic factor palliative in pernicious anemia can be obtained from yeast as well as from meat, thus suggesting that it is closely related to vitamin B. This choice will meet with general approbation. In thus honoring Dr. Castle, the College does honor also to the memory of him for whom this prize is named.

ECONOMIC ASPECTS OF TREATING SYPHILIS ADEQUATELY

The major responsibilities of the physician in the effort to control syphilis are those of making an early diagnosis and of then administering adequate treatment. While he cannot ignore the value to public health of educational methods of prophylaxis, and of various other measures in which he may be required to participate actively, upon the physician rests the responsibility of rendering his pa-

tient non-infectious as expeditiously as possible and then preventing or at least mitigating, that long series of disasters which hang, shadow-like, over his subsequent existence. If in the time of prosperity it was difficult to secure for the patient with freshly acquired syphilis that continuity of treatment which he so greatly needs, how much more difficult is it today! In a symposium on "Syphilis as an Economic Problem", appearing in the October number of the *Journal of Social Hygiene* Bromberg¹, Davis,^{1,2} and Snow³ have treated this question in a manner so thought-provoking that it commands the fullest attention. There can be no better argument for the necessity and inestimable value of a long continued intelligent, cooperative physician-patient relationship.

The magnitude of the economic problem involved becomes apparent at once when two facts are brought together. The first of these is that it has been estimated by competent authority upon studies conducted in many parts of the country by the United States Public Health Service,

¹BROMBERG, LEON and DAVIS, M. M.:
The cost of treating syphilis. *Am. J. Hyg.* 1932, LXIII, 365-375.

²DAVIS, MORRIS M.: The cost of syphilis to pay for the treatment of it.
J. 1932, 381.

³SNOW, WILLIAM L.: A study of the cost of syphilis treatment.
Am. J. Hyg. 1932, 381.

that there are about 500,000 new cases of syphilis in the United States every year. The other is that the average cost of one year of treatment of early syphilis, according to the continuous scheme of therapy recommended by the United States Public Health Service, varies from \$268.00 to \$1,050.00 depending upon whether the fee-bill used is that of a good general practitioner or of the more exclusive type of specialist in this field. Even when the cost is computed according to the schedules of two "pay clinics", set up with salaried physicians and organized on a basis intended to make them no more than self-supporting, it amounts to \$133.50 in one instance, and to \$169.50 in the other. The scheme of therapy referred to was the result of the collaboration of six outstanding syphilologists. While they emphasized that each patient must be treated individually, less than the stated amount of treatment would rarely be considered adequate and changes in the plan of procedure would not materially affect the totals. The recommended medical services for the adequate management of a case of early syphilis during the first year include two physical examinations, twenty-six injections of arsphenamine or neoarsphenamine, twenty-six bismuth or mercury injections, eight serological blood tests and one examination of the spinal fluid. (The reader can readily compute the total cost according to the current charges of his own locality.)

When representative cases were selected from seven different clinics in order to ascertain the precise medical services which had been rendered it was found that at minimum private office

rates the average cost of treatment for one year would have been \$314; at specialists' rates, \$715. These, again, were early cases; for the treatment of latent syphilis and of neuro-syphilis, the expense is, on the average, considerably higher.

It is recognized that a minimum figure of \$300 does not represent an average of what private patients actually pay for a year's treatment of syphilis. Much of the treatment may be on a charity, or semi-charity basis, the doctor may not administer the recommended courses of medication; or, most frequently, the patient will cease treatment even before the first year is completed. No one can deny that for the treatment outlined, the minimum figures are reasonable. Likewise from the patient's standpoint, the potential benefits that may be derived from adequate treatment make the cost seem trivial. The relation between this cost and the ability of various groups of the population to pay it is another question.

The ability of the patient to pay for adequate treatment of recently acquired syphilis is adversely affected by several special considerations. Since continuity of treatment throughout several years is essential, ability to pay for the initial blood test and for a few intravenous injections is of but little significance. Recently acquired syphilis is most prevalent among young persons between sixteen and thirty years of age when earning power is comparatively low. The feeling of shame and resulting desire for secrecy makes the individual unwilling to inform his family of his difficulty. Thus he is unable to draw upon the resources of

those who would be only too glad to aid him if he had suffered an injury or had acquired a disease unassociated with a social stigmatization. On the other hand the ability of the patient to pay is favorably influenced by the prolonged period of treatment, in that a series of payments may be made rather than a single sum. There is an inherent difficulty here, however. If, after a few weeks of treatment, there are no disturbing signs or symptoms of his disease, the patient is very apt to feel unable, as well as unwilling, to make a further investment in treatment.

Statistical studies by Davis² bring out clearly that for over 80 per cent of the population the minimum cost of treatment of syphilis at minimum private rates would take over ten per cent of their total incomes. While such a proportion may be expended without hardship by those in the higher income groups, from a total income of \$2,000 or less such an amount cannot be withdrawn without cutting into the necessities. For the single man, just starting out as an independent economic unit, with a salary of \$1,200 or less, the difficulty is equally great. From his analysis of the situation, Davis came to the conclusion that at the present time about 80 per cent of the population cannot pay for adequate care of syphilis at private rates and fully one-third of the population, if infected, must re-

ceive treatment for syphilis free or for nominal charges. Thus it must be true that the cost is an important cause of insufficient or inadequate treatment, but practically, it is in all probability a less important cause than is carelessness or indifference on the part of the patient himself.

It is an unthinkable situation that for financial reasons alone the syphilitic cannot receive that treatment which he needs. Not only the welfare of the individual but the health of the community demands that such must not be the case. It is easier to state the problem than to find the solution. That there must be close cooperation between the medical profession and the public health agencies is obvious. Here, as in other problems of medical economics, the medical profession must recognize the need and give understanding aid in arriving at a solution. It seems clear that in different parts of the country, urban and rural and for different economic groups, varying provisions must be made. The medical profession should lead in planning effective action. There can be no doubt that if other solutions are not found pay clinics and free dispensaries with their attendant evils, must be set up to meet this need, and as previously emphasized a protracted sympathetic co-operative physician-patient relationship, never to be found in the pay clinic or dispensary, is the great need of the patient with syphilis.

Abstracts

The Differential Diagnosis of Primary Neoplasms of the Mediastinum By CUSHMAN D HAAGENSEN, M D (The Am Jr of Cancer, 1932, xvi, 723-782)

The following classification of primary neoplasms of the mediastinum is proposed

A Malignant

1 Lymphosarcoma

- (a) Small round-cell lymphosarcoma (malignant lymphocytoma)
- (b) Large round-cell lymphosarcoma (reticulum-cell lymphosarcoma)

2 Hodgkin's disease

3 Leukemic lymphoma

4 Leukosarcomatosis

5 Thymic carcinoma

B Benign

1 Dermoids

2 Other cysts, including echinococcus cysts and ciliated epithelial cysts

3 Ganglionic neuromas and neurofibromas

4 Benign connective-tissue tumors including fibroleiomyomas, fibromas, chondromas, and lipomas

Since determination of the tumor type by biopsy is rarely possible, although classification is necessary in order to guide therapeutic management and determine prognosis recourse must be had to differential diagnosis upon clinical evidence. As to age, thymic carcinoma usually occurs at a much more advanced age than other malignant neoplasms of the mediastinum. Large round-cell lymphosarcoma and Hodgkin's disease most often occur in patients between 20 and 30. Small round-cell lymphosarcoma (malignant lymphocytoma) usually affects infants. In this age group many dermoid cysts also occur. The direction of symptoms is also a very important consideration in differential diagnosis. If a patient has a long history of cough and dyspnea, it is probable that the process is benign. Clinical signs and symptoms, while extremely important in making the diagnosis of mediastinal tumor, frequently are of but little value in differentiation of types. Roentgenographic diagnosis of primary neoplasms of the mediastinum may be rendered difficult by the similar and sometimes identical images produced by aneurysm of the aorta, retrosternal goiter, idiopathic dilation of the esophagus, cold abscess of the vertebrae, tuberculosis of the mediastinal lymph nodes, encapsulated mediastinal pleurisy, mediastinal abscess, lung abscess adjacent to the mediastinum, hydatid cyst, carcinoma primary in a portion of lung adjacent to the mediastinum, and metastatic carcinoma of the mediastinum. Here aneurysm is the chief difficulty. As to roentgenotherapeutic response in differential diagnosis, lymphosarcoma, Hodgkin's disease, leukosarcoma, and leukemic lymphoma are often strikingly radiosensitive, although occasional radioresistant cases are found. Thymic carcinoma and the various benign neoplasms of the mediastinum are radioresistant.

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Parotid hypertrophic, ein Symptom des Diabetes Mellitus [Hypertrophy of the parotid glands a sign of diabetes mellitus] By ERNST FRAUM (Klin Wochenschr, 1932, xi, 1704-1705)

The investigation forming the basis of this paper had its origin in the observation of symmetrical enlargement of the parotid glands in an elderly woman which was without pain, fever or any other evidence suggesting an inflammatory character. It showed exacerbations between which the glands did not return to normal size. After some years this patient was found to have diabetes mellitus of a moderate grade of severity. Particularly during the periods of more marked enlargement of the parotid glands a characteristic facial configuration

was observable. A similar facial character was found to be common among diabetics, and palpation showed that the fullness in the parotid regions was due to an increase in gland substance and not to pads of fat. Conversely, of 27 patients selected because of enlargement of the parotids, 16 were found to have a definite glycosuria on an unrestricted diet and the fused blood sugar curve of the remaining 11 was of the type considered characteristic for latent diabetes. It is particularly in the sthenic constitutional type, with a tendency to obesity, a strongly developed skeletal system, arterial hypertonicity, enlargement and induration of the liver and arthritic phenomena, that the characteristic change in the parotid glands is observable. The association of this sign with glycosuria was noted by Hess in 1918, and with obesity, by Sprinzels in 1912. Observations of this nature furnish new supporting evidence of ancretory function on the part of the parotid gland, the hypertrophy of which may well be of a compensatory nature. Recognition of this sign should prove of value in the early diagnosis of diabetes in the constitutional type described.

The Occurrence of Sicklemia in the White Race. By SAMUEL ROSENFELD, M.D., and JOSEPH B. PINCUS, M.D. (*Am. Jr. Med. Sc.*, 1932, *clxxxiv*, 674-682.)

It is generally believed that sickle cells occur only in the blood of the negro or in those with an admixture of negro blood. The incidence of the sickling trait among unselected negroes seems to be about 7 per cent. This trait is hereditary and is transmitted as a Mendelian dominant. The literature alleging the occurrence of sicklemia in white persons has been reviewed, keeping in mind that the chief sources of error lie in mistaking other deformities of the red blood cells for sickling or in failure to exclude the possibility of admixture of negro blood in cases with true sickling. With these possibilities in mind most of the alleged cases of sicklemia in white patients may be eliminated. Only one previous case, that of Cooley and I.e., in a white child of Greek descent, is free from reasonable suspicion. The case reported by Sights and Simon is considered to be supported by data too in-

complete for any conclusion as to its validity. A new group of cases is reported in this paper in which the sickling trait has been definitely shown to be present in three generations of an Italian family, which has been positively without admixture with the colored race for five generations. Moreover this family came from a region in Italy in which negroes are practically unknown. While this evidence would seem to indicate that this anomaly of the blood occurs in other than the negro race, the possibility cannot be absolutely ruled out that in some remotely previous generation there might have been a negro ancestor with sickle cells in the blood. Through dominant inheritance, the sickling trait might have been handed down to white descendants showing no external trace of negro features. Whatever the explanation may be it is obvious that this anomaly will be encountered from time to time in those who are of the white race as far as can be ascertained.

On the Transmission of Huntington's Chorea for 300 Years—the Bures Family Group. By P. R. VESSIE, M.D. (*Ir. Nerv. and Ment. Dis.*, 1932, *lxxvi*, 553-573.)

Through study of the earliest colonial records the author has ascertained that a group which emigrated from Bures, Suffolk, England, in 1630, has contributed very largely to the incidence of hereditary chorea in this country. Approximately 1000 cases of Huntington's chorea have been collected from the direct and collateral lines of this group which consisted of three men and their wives. The social problems of this group and the more immediate descendants show why the choreic affliction was reputed disgraceful and viewed with terror in succeeding generations. The witchcraft literature and records of court procedures indicate the extent to which the violent motions and agitations of the body played a part in arousing suspicion of witchcraft. In these interlocking conditions there has been a transmission of the chorea, now known as Huntington's, for 300 years and 12 generations since their emigration to the New World. The family has been isolated, persecuted and persistently threatened with extermination without abatement of the disease.

Reviews

Special Cytology The Form and Functions of the Cell in Health and Disease A Text-book for Students of Biology By FORTY-SIX CONTRIBUTORS Edited by EDMUND V COWDRY, Washington University, St Louis, Missouri Second edition In three volumes xxiv + 1838 pages, 757 illustrations Paul B Hoeber, Inc, New York 1932 Price, \$30 00 for three volumes

The second edition of *Special Cytology*, edited by E V Cowdry, has been strengthened by generous revision, covering the progress of research during the three or four years which have elapsed since the first edition was prepared Fourteen new contributors have filled in some of the gaps in the list of subjects treated That such lacunae must exist is inevitable, for the extent to which the structure of the human body may be subdivided for purposes of description and original investigation is all but unlimited As with all similar compilations, the very item of information which is sought for, may yet be wanting in spite of this expansion This three volume work has several especially commendable features One is the excellent mechanical book-making shown, with an unusual freedom from minor errors (The reviewer cannot refrain, however, from calling attention to the misspelling of 'taradise' on pages 182 and 183) The contributors, to a remarkable degree have entered into the general spirit of the work in that they have been more concerned in being interpreters of their respective fields of investigation than in presenting individualistic views Finally, the bringing together, as is seriously attempted in some chapters, of normal and pathological cytology is a new and extremely worthwhile endeavor More complete utilization of this principle ought to be made

Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, Gynecologist to Mt Sinai and to Northern Liberties Hospitals, Philadelphia and LEOPOLD GOLDSSTEIN, M D, Demonstrator of Obstetrics, Jefferson Medical College, Assistant Gynecologist to Mt Sinai Hospital, Formerly Fellow in Gynecologic Research, University of Pennsylvania, Philadelphia, 518 pages with 117 illustrations W B Saunders Company, Philadelphia and London 1932 Cloth, \$6 00

Clinical Endocrinology of the Female is written by gynecologists and the subject matter is presented chiefly from the point of view of that specialty Each of the glands of internal secretion, ovary, pituitary, thyroid, adrenal, parathyroid, thymus, pineal gland and pancreas, is thoroughly discussed in regard to its histology and physiology, and just how the hormone or hormones of each is tested for in actual practice The interrelation of these glands and the effect of this interrelation upon the female is considered from every angle

There is not the slightest doubt that a knowledge of endocrinology is of tremendous importance and the authors stress the fact that many young women, who previously would have been subjected to needless surgery, are now being successfully treated by gland therapy This type of therapy is gradually being increased, as more and better standardized extracts become available Thyroid and pituitary extract have, of course been on the market for some time, as has also suprarenal cortex and insulin It is to be hoped that Hartman's "cortin" will soon be produced in sufficient quantities to relieve some of the terrific exhaustion of Addison's disease It is now possible to secure active estrin (lipoal ovarian extract) and active pituitary sex hormone, the latter of which is a cordial to the authors, I

almost specific in the treatment of functional uterine bleeding. They believe that "functional uterine bleeding, regardless of the age of the patient, is due to the continued and unopposed action of oestrin on the endometrium, producing what is commonly called 'endometrial hyperplasia'. The underlying cause is a follicle cytolysis, which results in the prolonged production of oestrin and an absence of the luteal hormone, progesterin." Progesterin, unfortunately, is not yet obtainable for therapeutic use.

Dr Mazer and Dr Goldstein state that "pseudomenstruation", the cyclic uterine bleeding without the presence of a premenstrual endometrium, is due to the failure of ovulation and luteinization, and is a frequent occurrence in regularly menstruating, sterile women, who are free from pelvic disease. They feel certain that many fertilized ova may be expelled, or aborted, because of the lack of a properly prepared endometrium upon which to attach themselves.

The significance and the technique of the Aschheim-Zondek test for pregnancy is given in detail, but the authors prefer the Friedman modification, using one rabbit instead of five mice because of the shorter time required for the test.

The book contains several interesting charts, a number of illustrations and there is also a very full bibliography.

Probably in order to stress the importance of the subject (or perhaps to make a thicker book) there is repetition to the point of making the book a bit tedious in spots. The repetition includes the illustrations, several of which are given twice, with different figure numbers and slightly different captions (Fig 14, p 42 and Fig 51, p 161; Fig 49, p 160 and Fig 97, p 394; Fig 50, p 161 and Fig 98, p 395). It is also rather confusing to read the report of the cure of Frohlich's syndrome, in a boy of seventeen, in a paragraph on low-dosage irradiation of the hypophysis, in the successful treatment of amenorrhoea and about a hundred pages farther on to find the same seventeen-year-old boy again reported in a paragraph on low-dosage irradiation of the pituitary gland in the treatment of pituitary obesity associ-

ated with menstrual disorders (P 307 and p 450).

This book contains much that is well worth while reading, upon a subject with which the medical profession in general should keep pace in order to treat patients more intelligently. R C W

Clinical Interpretation of Laboratory Reports By ALBERT S WELCH, A B, M D. Clinical Instructor in Medicine in the University of Kansas School of Medicine in Kansas City, Kansas, Director of the Laboratory of the Alfred Benjamin Dispensary, and Attending Surgeon of St Joseph's Hospital in Kansas City, Missouri, formerly Pathologist to the Kansas City General Hospital, and Chemist to the Coroner of Jackson County. 332 pages, 16 illustrations. P. Blakiston's Son and Co., Inc., Philadelphia. Price, \$4.00, net.

This book is divided into sixteen chapters, one each being devoted to a consideration of the laboratory examination of urine, blood smears, cultures, cerebro-spinal fluid, gastric and duodenal contents, feces and sputum. The remaining chapters are given over to a consideration of blood chemistry, serology, tissue examination, the basal metabolic rate, the electrocardiogram, forensic and special tests. There is probably a need for a conveniently arranged text dealing with the clinical interpretation of reports based upon complicated (and simple) laboratory procedures. This text however fails to measure up to the criteria the reviewer considers necessary for the consummation of its purpose. In his preface the author quite properly warns clinicians to choose their laboratory with discretion and to discriminate between really large laboratories and the equally reliable ones. And yet throughout the text the reader cannot fail to be impressed by the author's only too evident dependence on laboratory tests and his frequent reference to reports rendered by the general and experienced worker. It seems a pity that a conscientious and experienced worker like the red blood cell, the white blood cell, the erythrocyte or the leucocyte, should be so completely overlooked in a book of this kind.

mistake leucocytes or erythrocytes passing in currents, for motile amebae. Nor should confusion be caused by cotton fibers when searching for actinomyces. In the chapter on tissue examination, the implication arises all too frequently of a final pathological diagnosis based solely on the gross appearances. Certainly no competent pathologist would care to append his name to a diagnostic sheet after merely a " cursory examination " of tissue clinically suspicious of actinomycosis (page 279), and carcinoma of the thyroid is not as rare as implied (p. 268), unless the diagnosis is rendered solely on the macroscopic changes. Other statements are equally misleading. Appendiceal carcinoids do not commonly suggest adenocarcinoma. Gelatinous carcinoma of the peritoneum cannot be an entity but must itself be secondary to a mucin-secreting carcinoma elsewhere in the body. Sarcoma in a lymph node can bear only an extremely superficial resemblance to actinomycosis (p. 273) and the two should no more be confused than should absorbing suture material be mistaken for tubercles (p. 276). It is by no means certainly established that a persistently negative Wassermann indicates cured syphilis. It seems doubtful that hair in the urine could often have a dermoid cyst for its source (p. 26) or that "lipoid carcinoma of the prostate may cause the appearance of doubly refractive lipoids in urine". Some passages suggest a distinctly iconoclastic attitude. It is not pleasing to read that "the fragility test is of little clinical value (because) there is as yet little therapeutically that can be done about it", or "it really makes little difference clinically whether the sarcomas of lymph glands without blood changes such as lymphosarcoma, sarcoma of lymph glands, or lymphosarcomatosis are distinguished from each other" (p. 273). Also, attempts to demonstrate spirochetes in tissues are very much worth while especially in primary lesions, despite the author's opinion to the contrary. An experienced observer would not mistake parts of the elastica of arteries for the *Trichomonas* and indeed he should be disappointed if he could not find them. The opportunity is lost to mention a few of the other organisms which

whether the section on forensic tests properly belongs in a book of this kind—the space could with advantage be used in enlarging other sections. Such addition should make the subject matter more readable. Without careful revision, this book cannot be recommended to its intended clientele. H. G.

The Cardiac Output of Man in Health and Disease. By ARTHUR GROLLMAN, Ph.D., M.D., Associate Professor of Physiology in the Medical School of the Johns Hopkins University. xiv+324 pages, 25 figures. Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland, 1932. Price, \$4.00, postpaid.

In the introduction the author states that this monograph is to deal with the variations of the cardiac output under different physiological and pathological conditions and the relation of these variations to other changes occurring in the circulatory system. In Part I he briefly outlines the methods that have been developed for determining success or failure in these methods and finally gives a comparison of the results obtained by various experimenters using them. Part II is devoted entirely to the Acetylene Method of determining cardiac output which, he says, has been proven accurate and is easily carried out. After deriving the algebraic formula used in calculating the cardiac output from the data obtained and describing the technique, the author gives proofs of the accuracy of the method and ends with a chapter on its applicability in clinical medicine. Part III is a discussion of the variations of cardiac output under many different physiological conditions. Tables and graphs giving data from numerous experiments are included. The application of cardiac output studies to pharmacology and therapeutics is discussed in Part IV. The opportunity offered by these studies for direct observation of the effects of drugs on the heart action in man is emphasized. The next few chapters take up the effects on the cardiac output of a number of drugs and other therapeutic applications which have been studied. Part V pertains to the clinical applications of cardiac output study, with the emphasis placed on disease of the heart and circulation. In

Part VI there is a short discussion of the correlation between cardiac output, metabolic rate, pulse rate, blood pressure and heart size. In the bibliography there are 483 references. This monograph represents an enormous amount of work and in it the author has carried out his purpose admirably in an interesting and understandable style. The subject matter, while of interest to the internist, should be particularly valuable to students of physiology and experimental cardiology. B M H

The Chemistry of Tuberculosis. A Compilation and Critical Review of Existing Knowledge on the Chemistry of the Tubercle Bacillus and Its Products, The Chemical Changes and Processes in the Host, The Chemical Aspects of the Treatment of Tuberculosis. By H GIDEON WELLS, M D, P H D, Director of the Otho S A Sprague Memorial Institute and Professor of Pathology in the University of Chicago, and ESMOND R LONG, M D, P H D, Director of the Laboratory of The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis, and Professor of Pathology, University of Pennsylvania, formerly Professor of Pathology in the University of Chicago. Second edition, thoroughly revised. iv + 481 pages. The Williams & Wilkins Company, Baltimore, 1932. Price, \$7.00.

The purpose and character of this book are set forth in the lengthy subtitle. It is, in fact, a rich storehouse of knowledge of the chemical attributes of tuberculosis in all its phases. This huge material is well organized, and critically analyzed, by the joint authors, who are better qualified than any others to do this task. Ten years have elapsed since the manuscript of the first edition was completed. Slow as progress may seem, the growth of knowledge during that period has necessitated a complete re-writing of the text. The present edition might well be considered a memorial to Dr Lydia M DeWitt co-author of the first edition, whose careful work and conservative interpretations are models of what experimental chemotherapeutic studies should be.

Her death, in 1928, kept her from realizing this revision which was anticipated in the preface of the first edition. Those engaged in striving to solve the problems of tuberculosis will find this book all but indispensable.

A Text-Book of Pathology. An Introduction to Medicine. By WILLIAM BOYD M D, M R C P Ed, F R C P Lond, Dipl Psych, F R S C, Professor of Pathology in the University of Manitoba, Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. 946 pages, 287 figures, one colored plate. Lea & Febiger, Philadelphia, 1932. Price, \$10.00.

On page 723 of this issue an excerpt from the preface of Boyd's Pathology is quoted. It well expresses the aim and spirit of this book—the systematic presentation of pathology in relation to the living patient. The plan of the book does not vary greatly from others of its kind which undertake to present both General and Special Pathology under one cover. It is well-written, with an excellent choice of both textual and illustrative material. The author is forced to be dogmatic for the sake of brevity. A teacher of pathology might well criticize the order of treatment since inflammation is the introductory chapter, while the extrinsic factors in the causation of disease are not considered until the seventh, eighth, ninth, eleventh, and thirteenth chapters are reached. For the practitioner, however, this difficulty will not appear and there is no hesitancy in recommending this as one of the best of the textbooks in Pathology in the English language.

Principles of Chemistry. An Introductory Textbook of Inorganic, Organic, and Physiological Chemistry for Nurses and Students of Home Economics and Life Chemistry. With Laboratory Experiments. By JOSEPH H ROE, PH D, Professor of Biochemistry, George Washington University Medical School, Department of Chemistry, Central School of Chemistry, Washington, D C. Captain, Surgeon, Division, U S Medical Reserve. Textbook, 486 pages, 50 illustrations. Price, \$10.00.

Mosby Company, St Louis, 1932 Price, \$2 50

That a third edition of Roe's textbook has been required demonstrates the usefulness of a work of this character. It differs from the elementary texts provided for high schools in the greater emphasis upon physiological chemistry, as indicated by chapters on Milk, The Blood, Digestion, Metabolism, Vitamins, Foods, Dietary Requirements and The Internal Secretions. It is well written and very well printed. The inclusion of considerable theoretical material not found in the earlier editions appears to make the treatment of the subject rather too heavy for the needs of the pupil nurse. Some teachers of nurses will choose to omit certain sections. Where not an assigned text, this book should be included in the training school library for reference.

Medizinische Praxis Band XIII, Blutkrankheiten [System of Medicine Volume XIII, Diseases of the Blood] By PROF. DR. HEINRICH SCHIFFCHT, Medical Direc-

tor of the Ebenhausen Sanatorium near Munich xii + 197 pages, 13 text figures and 2 plates in colors. Theodor Steinkopff, Dresden-Blasewitz, Residenzstrasse 32, Germany 1932 Price in paper, RM 13 80, bound, RM 15

This book follows the general plan of practical texts on the blood and diseases of the blood. The first section of 37 pages deals with technical methods, including the numerous newer procedures not in the armamentarium of many whose student days are now well in the past. The second section of about the same size describes systematically the formed constituents of the blood. The remainder is concerned with the diseases of the blood and blood forming organs, and with the changes in the blood associated with various morbid states. This is a clearly and compactly written book, and thoroughly up-to-date. Even ovalocytosis has been included, although the mention is brief. For those reading German readily, this will prove a very useful manual.

College News Notes

NOMINATIONS FOR ELECTIVE OFFICERS 1933-1934

The Nominating Committee herewith transmits the following nominations for elective officers of the American College of Physicians for the year 1933-34:

President-Elect—Jonathan C. Meakins,
Montreal, Canada

1st Vice President—Maurice C. Pincoffs,
Baltimore, Md.

2d Vice President—Charles G. Jennings,
Detroit, Mich.

3rd Vice President—Noble Wiley Jones,
Portland, Ore.

Respectfully submitted,

J. H. Meyer, Chairman

Ernest B. Prindle

E. J. G. Pennington

W. C. E. Wright

Dr. James M. Anders (Master) read a Memoir on Dr. Hiram Corson before the Section on Medical History of the College of Physicians, Philadelphia, on October 10.

Dr. Anders also read a paper on "The Modern Health Movement" before the Philadelphia County Medical Society on October 26, Pennsylvania Health Day.

On the evening of November 5, Dr. D. Schuyler Pulford (Fellow), of Sacramento, addressed the Placer County Medical Society at its meeting held at the Weimar Sanatorium. Dr. Pulford's address, which was illustrated by lantern slides, was on "The Never Developments: Diagnosis and Treatment of Cancer."

An announcement is made of the following:

gifts to the College Library of publications by members

Dr Carl V Vischer (Fellow), Philadelphia, Pa—1 book, "Pulmonary Tuberculosis".

Dr Jacob M Cahan (Fellow), Philadelphia, Pa—1 reprint,

Dr W W Chrisman (Associate), Macon, Ga—2 reprints,

Dr Nathan Smith Davis, III (Fellow), Chicago, Ill—2 reprints,

Dr Charles F Fisher (Fellow), Brooklyn, N Y—1 reprint,

Dr Alvis E Greer (Fellow), Houston, Texas—2 reprints,

Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,

Dr Charles C Hinton (Fellow), Macon, Ga—2 reprints,

Dr E W Phillips (Fellow), Phoenix, Ariz—2 reprints,

Dr H L Arnold (Fellow), Honolulu Hawaii—1 reprint,

Dr Ellen C Potter (Fellow), Trenton N J—6 reprints,

Dr Karl Rothschild (Fellow), New Brunswick, N J—1 reprint,

Dr Edward W Schoenheit (Fellow), Asheville, N C—18 reprints

Dr John Dudley Dunham (Fellow), Columbus, Ohio, addressed a joint meeting of physicians and dentists at Hotel Warden, Newark, Ohio, October 27, on "The Interdependence of the Medical and Dental Profession"

At the meeting of The Yorkville Medical Society of the City of New York on November 21, Dr Albert S Hyman (Fellow) New York, spoke on "Recent Advances in the Study of Angina Pectoris" and Dr Joseph B Wolfe (Associate), Philadelphia on "The Use of Heart Hormone (Tissue Extract Substance) in Angina Pectoris". Dr John Homer Cudmore (Fellow), New York, and Dr George I Swellow (Fellow), Brooklyn, took part in the discussion

Dr Lewis I Moorman (Fellow) Oklahoma City is the author of a new section in Oxford Medicine (Volume 4, Part 2) on 'Industrial and Domestic Gas Hazards Aris-

ing through the Production, Refining and Consumption of Petroleum and Its Products"

Dr Clifford J Barborka (Fellow), for eleven years a consultant physician of the Mayo Clinic, has accepted a position in the Department of Medicine in Northwestern University, and has opened a diagnostic suite for the practice of Internal Medicine at 700 N Michigan Avenue, Chicago

Dr Barborka delivered two lectures, one "Diet in Health and Disease", the other "Dietary Regime in Cardiovascular Renal Disease", at the Oklahoma City Annual Fall Conference. On November 10 he addressed the American Dietetic Association on 'The Present Status of the Ketogenic Diet and Its Use'

Dr Ralph Pemberton (Fellow), Philadelphia, addressed the Academy of Medicine of Des Moines, Iowa, on the subject of 'Arthritis' on November 4, 1932. He addressed the Academy of Medicine of Cincinnati, Ohio, November 14 1932 on "The Newer Outlook of Arthritis"

Dr Martin H Collier (Fellow), Superintendent of the Lakeland Sanatorium, Grunloch, N J, was elected President of the New Jersey State Tuberculosis League at the Twenty-sixth Annual Meeting of that organization held recently in Newark, N J

Dr John I Marker (Fellow) Davenport Iowa was promoted to Lieutenant Colonel of the Medical Reserve Corps October 4 1932

Dr Arthur C Morgan (Fellow) Philadelphia addressed meetings in Erie, Pa.,burg, Clearfield and St Mary's Pa. in connection with the observation of Heart Day in October 1932

Dr William Henry Wirt (Fellow) Boston presented a paper on 'The North Side Practice of the Medical Society recently. Dr Wirt was in charge of preparing the paper on the subject of the 'The North Side Practice of the Medical Society recently'

Physical Therapy, held at Philadelphia, October 12-14, 1932

Dr E J G Beardsley (Fellow), Philadelphia, Pa, addressed the Staff of the Lancaster County Hospital Association, Lancaster, Pa, October 20, upon "The Diagnosis of Cardiovascular Disorders" Dr S S Simons (Associate), Lancaster, Pa, presided

Dr Beardsley was also the guest speaker at the Staff Meeting of the Glen Gardner Sanitarium, Glen Gardner, N J, October 21, his subject being, "Conditions that Commonly Simulate Pulmonary Tuberculosis"

Dr Louis F Bishop (Fellow), New York City, has been assigned to the Standing Committee of the New Jersey College of Pharmacy The College is in process of organizing a four-year pre-medical course

Dr Claude E Forkner (Fellow), formerly Assistant Physician to the Thorndike Memorial Laboratory, Boston, is now in Peiping, China, as Associate Professor of Medicine in the Peiping Union Medical College

Dr Howard T Karsner (Fellow), Cleveland Ohio, Professor and Director of the Institute of Pathology of Western Reserve University, has been elected the United States member of the Comité Directeur of the International Society for Geographic Pathology

Dr Hans Reese (Fellow), Madison, Wis, was elected President of the Central Neuropsychiatric Association at their annual meeting at Rochester, Minn, October 6-8, 1932

Dr S A Slater (Fellow), Worthington, Minn, Superintendent of the Southwestern Minnesota Sanitarium addressed the Plymouth County Medical Society at LeMars, Iowa, October 4, on "The Diagnosis of Pulmonary Tuberculosis"

Dr Slater also was the chief speaker at a meeting of the Woodbury County Medical Society at Storm Lake, Iowa, October 19

Dr E J G Beardsley (Fellow), Philadelphia,

Ga, was elected President of the Fifth District Medical Society of the State of Georgia on October 12

Dr John G Young (Fellow), Dallas, Texas, addressed the West Texas District Medical Society, October 4, on "Sinus Disease and Its Relation to the Child"

Dr Hyman I Goldstein (Associate), Camden, N J, read a paper entitled, "The Relation of Heart Disease,—Cardiac Murmurs, Angina Pectoris and Coronary Thrombosis,—to Gallbladder Infections and Gallstone Disease", before the Medical Section of the Congrès International de la Lithiase Biliaire at Vichy, France, September 20 Dr Goldstein also attended the annual sessions of the XXII Congrès Français de Médecine, October 10-11, at Paris

Dr Curren Pope (Associate), Louisville, Ky, addressed the staff meeting of Dr Anthony's Hospital at Louisville, Ky, on "Clinical Observations upon Pyretotherapy", on October 11

Dr Marjorie E Reed (Associate), Plymouth, Pa, is the author of a paper entitled, "Sydenham's Chorea, Diagnosis and Treatment", which appeared in the July number of the Medical Woman's Journal

Dr Clyde Brooks (Fellow), New Orleans, La, Professor of Physiology at the Louisiana State University Medical Center, New Orleans, has been selected to head the new department of Pharmacology and Experimental Therapeutics at that institution

The Oklahoma City Clinical Society conducted its annual fall clinical conference October 31 to November 3, under the presidency of Dr Ray M Balyeat (Fellow).

Dr Walter F Donaldson (Fellow), Pittsburgh, Pa, has been re-elected Secretary of the Medical Society of the State of Pennsylvania That organization will hold its 1933 meeting in Philadelphia

Dr Della W Bennett (Associate), San Francisco, Calif, has been appointed Director

of the Student Health Service at the University of California

Dr Philip F Barbour (Fellow), Louisville, Ky, was installed as President of the Kentucky State Medical Association at its annual meeting in October

Dr Lawrason Brown (Fellow), Saranac Lake, Dr Ralph Pemberton (Fellow), Philadelphia, and Dr Martin E Reyfuss (Fellow), Philadelphia, appear on the list of lecturers in connection with the 1932-1933 program of the William Harvey Society at Tufts College Medical School, Boston

Dr John T Murphy (Fellow), Toledo, Ohio, was elected President of the American Roentgen Ray Society at its recent annual meeting in Detroit

A program on the History of Physical Diagnosis was offered by the College of Physicians of Philadelphia, Section on Medical History, November 14, 1932, on the occasion of the College's Sixth Annual Students' Night Dr Thomas B Fitcher (Fellow), Baltimore, by invitation, gave an address on "Physical Diagnosis between Laennec and Roentgen", Dr Wm Egbert Robertson (Fellow), Philadelphia, gave an address on "Later Additions to Physical Diagnosis"

OBITUARIES

DOCTOR CHARLES G LUCAS

Dr Charles G Lucas (Fellow), Louisville, Kentucky, died at the St Joseph Infirmary, July 7, 1932, of thrombosis of the cystic artery with peritonitis

Dr Lucas was born in Cincinnati, Ohio, in 1870, his premedical education was obtained in the public schools of Louisville and he graduated from the Medical School, University of Louisville, in 1890. Locating in Louisville, he engaged in general practice for thirteen years as an associate of the late Dr John A Ouchterlony. In 1904 and 1905 he studied Gastro-Enterology in Europe and on returning to Louisville confined his work to that specialty. He held some teaching connection with the Medical School of the University of Louisville until the Department of Gastro-Enterology was established in 1915, when he became the head of that department and held that position until his death. He was a member of the Staff of the Louisville

City Hospital and the St Joseph Infirmary, he was serving as President of the latter hospital staff for the year, 1932. He was a member of the Jefferson County Medical Society, the Kentucky State Medical Association, the American Medical Association, the American Gastro-Enterological Association, (President, 1926, Secretary, 1930-1932) and the American College of Physicians (Regent, 1922-1923, and 1925-1928). He was a communicant of the Catholic Church and a member of the Pendennis and Louisville Country Clubs. He served in the Medical Department of the Army during the Great War, being stationed at Camp McArthur, holding the rank of Major on discharge at its close.

His was both an inquiring and acquisitive mind, while the field of purely scientific medicine was a familiar environment the art of his profession found him a skilled clinician; his interest in the one did not lure him from the bedside contact of the other.

pleasure in the solitude of intellectual pursuit never deprived him of the joy of the personal contact with the victim of ill health. While the masters in medical literature found a gracious and understanding welcome in his library, the sufferer of one of the ailments considered in these theses learned from him that "Medicine is an art that sometimes cures, often relieves, and always comforts" His manner was pleasing, his nature optimistic, his friendships unusually loyal, and on his going he left a reputation unsullied by selfishness and petty ambition He had an abiding faith in his religion and he lived the Golden Rule as his code of ethics as nearly as humanly possible He will be missed and mourned alike by faculty, friends and patients

(Furnished by VIRGIL E. SIMPSON, M.D., F.A.C.P., Louisville, Kentucky)

DOCTOR CARL VICTOR VISCHER

Dr. Carl Victor Vischer (Fellow), one of the younger but much respected and admired physicians of Germantown, Pennsylvania, died, November 15, 1932. His untimely death, after a month of painful, distressing and, from its inception, obviously hopeless illness occurred as the result of a septic process initiated by an osteomyelitis that had been in existence, without manifest symptoms, for a number of years.

Dr. Vischer's life, judged by the highest ethical standards, was a signal success. He was respected, admired and deeply loved by those who knew him best. His happy, cheerful and optimistic personality and his professional life of conscientious industry, combined with unremitting study, caused

him to be regarded by well-informed members of his profession as an admired and trusted colleague. Dr. Vischer lived an unselfish, admirable and useful life. He radiated an atmosphere of cheerfulness, happiness and hope that the world, especially the medical world, needs at all times, but, perhaps, never more than at present.

Dr. Vischer was born in Philadelphia in 1896, the son of a talented and much admired homeopathic surgeon. The son inherited those traits and characteristics that made his entrance into the medical profession the natural course for him to adopt. He graduated from his father's Alma Mater, the Hahnemann Medical College of Philadelphia, in 1919, when twenty-three years of age. After serving the Hahnemann Hospital as interne, Dr. Vischer continued to interest himself in the welfare of the Hahnemann Medical College and Hospital, and, as a result of his ability, faithfulness and industry, he was gradually advanced in rank, until at the time of his death, he was Associate Professor of Medicine in the College and Associate Physician to the Hospital. Dr. Vischer was Chief of the Outpatient Medical Department of the same institution for many years. This position afforded him a wealth of experience in clinical medicine. As a result of this experience, Dr. Vischer published a number of meritorious articles in current journals. These well illustrated his desire to share with others the practical knowledge that he had acquired. Dr. Vischer recently published a Handbook on Pulmonary Tuberculosis, which embodied the results of his studies in this disease.

He was deeply interested in all phases of medicine, but was best known for his interest in the disorders of the circulatory and respiratory systems. He was greatly interested in the practical phases of the control of pulmonary tuberculosis, and had been Associate Director of Devitt's Camp for tuberculous patients for a number of years.

Dr Carl Vischer's all too brief professional life of thirteen years was well and wisely spent. His temperament and inclinations prevented him from making the all too common error of youthful physicians of magnifying the importance of a knowledge of disease and minimizing the necessity of studying the patient and his reactions.

Dr Vischer was an enthusiastic believer in and a loyal supporter of so-called organized medicine. Early in his medical career, he affiliated himself with the local, state and national homoeopathic societies, and later, with the breadth of view that was as admirable as it is unusual, he also associated himself with the organizations of the so-called regular school. He was elected a Fellow of the American College of Physicians in 1928, and, in his characteristic wholesouled manner, interested himself in the healthy growth and development of the organization. He attended every Clinical Session of the college after his election, and many Fellows throughout the College will be saddened as are his Philadelphia colleagues, by the loss of this vital and charming personality.

(Furnished by E J G BRADLEY
M D, F A C P, Governor for eastern
Pennsylvania)

DOCTOR JAMES MANARA RECTOR

Dr James Manara Rector (Fellow), Columbus, Ohio, died September 17 1932, from a cerebral hemorrhage.

Dr Rector was born at Circleville Ohio, June 27, 1877. He was educated in the public schools of Circleville, and in 1903 was graduated from the Medical College of the Ohio State University. He later did postgraduate work at the Chicago Postgraduate College and at the New York Postgraduate Medical School. For many years, Dr Rector had been a member of the staff of Grant Hospital. During the Spanish-American War, he served in Cuba and Porto Rico, and was President of Battery H, Spanish War Veterans. He was a member of the Columbus Society of Internal Medicine, the Columbus Academy of Medicine, the Ohio State Medical Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1930.

DOCTOR JOSEPH WESLEY MALONE

Again we are called upon to turn our thoughts with respect to one of our associate members, Doctor Joseph Wesley Malone who died September 10, 1932.

Doctor Malone was born in 1866 and was prepared for the College of Physicians and Surgeons of New York at the Elizabeth Normal Academy of Pennsylvania. He graduated in medicine in 1888, and thereafter spent his entire life in the practice of medicine in Brooklyn. There, by industry, ability, and personality he came into the

recognition he deserved. He soon limited his practice to internal medicine and continued to keep abreast with the many advances in that specialty. With this progressive spirit, which kept him delving into the newer fields, he became in later years greatly interested in the allergic diseases. His ability, his fairmindedness, and his friendly understanding are the factors that soon claimed for him the recognition of the hospitals of the city. He was Attending Physician in Kings County Hospital; Attending Physician, Victory Memorial Hospital; and a member of the Courtesy Staffs of the Caledonian and St. John's Hospitals. During the World War he sensed his obligations to his country and gave his time as physician to the Local Board, No. 59, with the rank of Major of the Medical Corps of the United States Army, which work he carried out with his accustomed fidelity.

Doctor Malone was not only interested in scientific medicine but was also an ardent supporter of organized medicine. He was deeply impressed with the idea that the solution of problems arising from the relationship of the public to medicine must be guided by the medical profession if these

problems are to be solved correctly. He spent much time in his local County Society and in the Medical Society of the State of New York in furthering this conviction.

Doctor Malone was a member and ex-President of the Bay Ridge Medical Society, a member of the Flatbush Medical Society, the Medical Society of the County of Kings, and of the Medical Society of the State of New York. He was a Fellow of the American Medical Association, and was ex-President of the Medical Guild of Kings County, and a member of the Association of Military Surgeons of the United States. In 1922 he was made an Associate of the American College of Physicians.

During his years of active participation in medical affairs Doctor Malone made many friends through his sincerity of purpose and the charity of his mind. His standards and ideals of medicine were recognized by all, and in his passing we realize that we have lost a distinguished gentleman from our community as well as a devoted physician and true friend.

(Furnished by LUTHER F. WARREN, M.D., F.A.C.P., Governor for eastern New York.)

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The Clinical Significance of Leucopenia with Special Reference to Idiopathic Neutropenia

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San Francisco, California

THE development of leucopenia without apparent cause in a previously healthy individual is a subject about which there has been considerable discussion in recent years. Leucopenia brought on by definite etiologic factors such as certain bacterial and protozoan infections, toxic chemicals, or destruction of the bone marrow by tumor processes is readily understandable. Here the problem is concerned chiefly with diagnosis, and eradication or alleviation of the primary cause. There are instances of leucopenia, however, that are not so readily explained, and in which the cause remains obscure. In the medical literature one may find such conditions designated as "granulopenia", "granulocytopenia" of unknown origin, or "idiopathic" neutropenia. Cases of leucopenia falling in this group warrant further investigation. During the past three years we have had opportunity to observe several cases of leucopenia

of this nature, and certain of these will be discussed in this paper.

Before discussing the clinical aspects of leucopenia, it is necessary to consider the polymorphonuclear leucocyte, its origin and various stages of development from youth to maturity. The progenitor of the granulocyte series is a cell in regard to the exact identity of which there still remain differences of opinion. The concept of Sabin¹ and her associates on leucogenesis, however, has somewhat clarified the situation, and offers a tenable hypothesis on cell development from the primitive form to maturity. Whether or not the erythrocyte and granulocyte arise from a common parent cell, it is generally accepted that leucopoiesis normally takes place outside the blood sinusoids of the bone marrow, and the granulocytes gain entrance to the capillaries through their own motility. According to the concept of Sabin, the primitive progenitor of the granulocyte arises from a reticular cell lining the sinusoids of the bone marrow, and from this stage passes through a series of transformations to the adult form. The next cell in order is the myeloblast,

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and from this point on, maturation is a matter of cellular differentiation consisting in nuclear indentation and lobulation. As the cells age, cytoplasmic inclusions appear and their presence and tinctorial differences may be detected through the use of appropriate stains. In the bone marrow the young granular forms are designated as myelocytes a, b, and c, and the metamyelocyte. Normally in the circulation the fully matured form of the granulocyte appears as the motile, polymorphonuclear leucocyte.

When the bone marrow becomes involved by disease, leucopoiesis is interfered with, and under certain conditions leucopenia develops. Improper growth, failure of development, and aplasia of the bone marrow may appear as intrinsic disorders, and the white blood cells, the red blood cells, and the platelets become reduced in number. On the other hand, there are conditions in which the bone marrow shows marked cellular overgrowth of the leucocytic series, but apparently there is retarded maturation and the granulocytes in the blood become reduced.

This brief review is essential to the proper understanding of the pathologic physiology of the cases to be presented.

In an effort to obtain some information concerning the clinical significance of leucopenia, its relation to various clinical conditions, and conditions of occurrence of benign leucopenia, a statistical study of 10,000 hospital records was undertaken. A summary of the observations is presented here in the form of table, and certain deductions are made from the figures obtained.

In order to divide properly the 10,000 cases into a leucopenic group, those with normal, and those with elevated leucocyte counts, the figure of 5,000 leucocytes per c mm of blood was accepted as being the low standard for normal. In most text books of medicine it is stated that individuals in whose blood there are found 5,000 leucocytes or less per c mm show a state of leucopenia.

FREQUENCY AND CONDITIONS OF OCCURRENCE OF LEUCOPENIA

There are few data available that concern directly the frequency of leucopenia. Roberts and Kracke², in a statistical study of 8,000 records of patients seen in private practice for the ten-year period between 1920 and 1930, recorded that leucopenia occurred in 1,881 or 23 per cent of their patients. These authors took 6,000 leucocytes per c mm of blood as the lower limit of normal.

The data to be presented have been derived from the records, exclusive of the outpatient department, of the University of California Hospital. Examination of the records was limited to those belonging to the Division of Medicine, and the results obtained, therefore, represent a cross section of the illnesses suffered by the patients entering a general medical service. Patients who were in for "overnight" observation or treatment, and in whose records there does not appear an adequate history, the results of a complete physical examination or the reports of the "routine" laboratory test are excluded from this series.

From January, 1920, until January,

1931, 10,000 case records were made and these form the basis of this study. A high percentage of the patients presented a definite diagnostic problem that required analysis through careful physical examination and laboratory studies. Accordingly, in the records of patients in whose blood there was found an inadequate number of leucocytes, there usually appeared two or more leucocyte counts. An analysis of the blood reports of 1,167 of the total

number of patients showed leucocyte counts of 5,000 cells or less per c mm. Thus, 11.67 per cent of the patients entering the medical wards during the eleven-year period were deficient in white blood cells.

In table I have been summarized the cases of leucopenia occurring in the medical records of the University of California Hospital, together with the percentage frequency of occurrence among the various disorders.

TABLE I

Number of Records Examined		10,000
Number with Leucopenia		1,167
Females with Leucopenia		611—52.4 per cent of cases
Males with Leucopenia		556—47.6 per cent of cases
CONDITION IN WHICH LEUCOPENIA OCCURRED	NUMBER OF CASES WITH LEUCOPENIA	PER CENT INCIDENCE OF LEUCOPENIA IN THE VARIOUS CONDITIONS
I		
		75 TO 100 PER CENT INCIDENCE
Influenza	137	100 per cent of cases
Typhoid fever	14	100 " " "
Brucelliasis (undulant fever)	7	100 " " "
Banti's disease (splenic anemia)	19	100 " " "
Aleukemic leukemia	9	100 " " "
Aplastic anemia	5	100 " " "
"Agranulocytic" angina	2	100 " " "
Arsphenamine intoxication	2	100 " " "
Pernicious anemia, in relapse	109	97 " " "
Malaria	29	82 " " "
Myxedema untreated	30	75 " " "
II		
		25 TO 75 PER CENT INCIDENCE
Sprue	4	57 per cent of cases
Hodgkin's disease	23	52 " " "
Arthritis, acute infectious	6	33 " " "
Jaundice, catarrhal	9	31 " " "
Cirrhosis of liver	22	26 " " "
Endocarditis, subacute bacterial	13	25 " " "
Lymphosarcoma	6	25 " " "
III		
		4 TO 25 PER CENT INCIDENCE
Septicemia, staphylococcus	2	22 per cent of cases
Hyperplasia of thyroid gland	54	22 " " "
Hemolytic jaundice, acquired	3	11 " " "
Tuberculosis (all forms)	57	21 " " "
Cholecystitis, chronic	60	17 " " "
Lead poisoning	3	13 " " "
Rheumatic valvulitis, chronic	18	12 " " "
Infectious mononucleosis	1	15 " " "
Arthritis, chronic infectious	9	10 " " "
Peptic ulcer	34	10 " " "
Lues (tertiary)	41	9.7 " " "
Arthritis, chronic hypertrophic	20	7.6 " " "
Diabetes mellitus	36	7.2 " " "
Pellagra	1	4 " " "

IV
MISCELLANEOUS

Conditions in which the Per Cent Incidence of Leucopenia was not Determined
Because of Difficulties Encountered in Classification

	NUMBER OF CASES WITH LEUCOPENIA
Neoplasms (all forms)	114
Arteriosclerosis	58
Tonsillitis, chronic	17
Colitis, chronic	13
Appendicitis	11
Nephritis, chronic	11
"Secondary" anemia	11
Cystitis, chronic	7
Sinusitis, chronic	6
Bronchitis, chronic	5
Thrombocytopenic purpura	5
Bronchopneumonia	2
Osteomyelitis, chronic	2
Measles (adult)	2
Peritonitis, chronic	1
Dysentery, amebic	1
Dysentery, bacillary	1
Allergy	1

V	
UNEXPLAINED LEUCOPENIA	
No diagnosis	70 cases 6 per cent of all cases of leucopenia
Nervous exhaustion	{
Neurosis, psychosis, hysteria	
	44 cases 3.7 per cent of all cases of leucopenia

From an examination of the table it will be noted that 52.4 per cent of the total number of cases of leucopenia occurred in females and 47.6 per cent of the cases in males. This indicates a moderately increased incidence of leucopenia in the female sex.

Data relative to the various conditions and different states of ill health in which leucopenia may be found of less frequent occurrence are listed in groups II, III, and IV. It will be observed that leucopenia occurred in very high incidence in a rather limited number of diseases set forth in group I. Of some interest is the appearance of numerous instances of leucopenia in patients with chronic disorders of one sort or another.

Clinically, the division of the idiopathic or obscure leucopenias into well defined groups presents a great difficulty because of lack of knowledge of

the etiologic factors concerned. However, there are cases of severe leucopenia that persist over a period of weeks or months. These are usually associated with other abnormalities of hematopoiesis, and are frequently fatal. These may be differentiated from cases in which the abnormality of leucopoiesis is less severe in degree. With these facts in mind two clinical groups of leucopenia of obscure origin may be defined.

I Malignant leucopenia of obscure origin.

II Benign leucopenia of obscure origin.

MALIGNANT LEUCOPENIA OF OBSCURE ORIGIN

The following cases are illustrative examples of conditions falling into this group.

Case I, Idiopathic Aplastic Anemia* J L T, a white, married, American farmer, aged 27, entered the hospital September 12, 1928, complaining of weakness and pallor. Except for pertussis at 6 years of age, chicken pox at 11, measles at 17, and bilateral mumps at 23 years of age, he had enjoyed good health for four years until the latter part of May, 1928. At that time a localized infection appeared on the back of his right hand, which, with surgical intervention, healed at the end of 3 weeks. About a month later, he began having signs and symptoms of anemia. A week prior to entry, small ecchymoses appeared on his legs following trivial trauma. He lost 10 pounds in weight during the month of June. The patient was undernourished and very pale. There were fading ecchymoses over both tibiae. Physical examination revealed no other abnormality.

Laboratory data The examination of the blood on September 12 showed erythrocytes 1,216,000 per c mm, hemoglobin, 29 per cent (S), color index, 1.2, hematocrit, 15 per cent of cells, reticulocytes, 0.4 per cent with a comparable number of polychromatic

cells. There were an occasional large and a few small erythrocytes. A few red blood cells were oval in shape and a few showed central pallor. The leucocytes numbered 2,500 per c mm of blood. Differential count: polymorphonuclears, 24 per cent, lymphocytes, 70 per cent, monocytes, 6 per cent. The platelets were greatly reduced. The bleeding time was 15 minutes. The coagulation time by the method of Lee and White was 15 minutes. No clot retraction occurred at the end of 3 hours at 37°C.

The basal metabolic rate was plus 65 per cent. The Kahn test on the blood serum was negative. Repeated blood cultures revealed no bacterial growth. Fractional gastric analysis showed the presence of free hydrochloric acid in normal amount.

A biopsy of sternal marrow was performed on September 13. This tissue was made up largely of fat cells. Small focal hematopoietic clusters of cells were scattered between the interstices of those cells, and only in one area was there a focus of apparent cellular activity as shown in figure 1. In these foci there were a moderate

*It is a pleasure to record our thanks to Doctor George R. Minot for the opportunity to study cases I and II at the Thorndike Memorial Laboratory of the Boston City Hospital, and to Doctor Frank B. Mallory of that hospital for the use of the autopsy material.



FIG 1 Specimen of bone marrow removed at biopsy from case I. Note small focus of hematopoiesis in an otherwise relatively bone marrow.

number of neutrophilic myelocytes and an occasional eosinophilic myelocyte, but in the entire specimen no adult granulocytes nor megakaryocytes were observed. The cells comprising the foci were chiefly erythroblasts and myeloblasts, among which an occasional mitotic figure was noted. The endothelial cells lining the sinusoids in the areas of hematopoiesis were of moderate size, but were small in the collapsed sinusoids. A few large phagocytic cells containing pigment were seen. Diagnosis: Aplastic bone marrow.

Course of illness. On September 19, small hemorrhages appeared in the retinae and the following day small petechiae were visible in the skin over different parts of the body. On September 22, 1928, the patient was given his first transfusion of blood. Liver pulp in amounts of 300 grams daily for a period of 10 days and a subsequent course of liver extract 343 N N R, derived from 600 grams of liver daily, failed to affect the bone marrow. Temporary relief was afforded by 6 transfusions of blood, 3 of which were given on 3 successive days prior to splenectomy. During the two and one-half months the patient was in the hospital, examinations of the blood were made at frequent intervals. The erythrocytes fluctuated between 600,000 and 1,000,000 per c. mm., depending chiefly upon transfusions of blood. The reticulocytes varied from 0.4 and 1.0 per cent. The leucocyte count varied from 1,700 to 2,500 per c. mm. The differential count remained essentially the same as at entry. On November 11, 1928, splenectomy was performed notwithstanding the diagnosis of aplastic anemia; there was a forlorn hope that the operation might favorably affect the patient. The spleen weighed 128 grams. Microscopical examination showed it to be normal except for slight enlargement of the malpighian bodies.

A week after splenectomy, petechial hemorrhages appeared over the body. The patient began to have frequent severe nosebleeds, grew steadily paler and weaker, and died November 22.

The autopsy showed an aplastic fatty bone marrow, the spleen of normal size and structure, and the lungs, heart, liver, and kidneys all normal. The lungs were normal except for the presence of a few small petechiae.

DISCUSSION

In this case, idiopathic aplastic anemia occurred in a previously healthy adult male 27 years of age. Neither exposure to overdoses of x-ray, radium, benzol, or arsenicals, nor some hidden focus of infection could be held as an etiological factor. The condition appeared to be an intrinsic abnormality of hematopoiesis, and failure in leucocyte, erythrocyte, and platelet production.

Of some importance, however, is the fact that apparently active but small foci of blood formation could be seen in the specimens of bone marrow removed at biopsy, an example of which is shown in figure 1. Among such clusters of cells a few mitotic figures were noted. Similar observations have been recorded by Mills.³ This evidence of hematopoietic activity holds forth hope of discovery of some substance, the administration of which will permit adequate erythrocyte and leucocyte growth.

Case II, Agranulocytosis, Esophagitis. I. W. S., a Jewish housewife, aged 47 years, was brought to the hospital on May 11, 1929, suffering from weakness, headaches, chills and fever. One of her mother's sisters had died of Hodgkin's disease at 50 years of age. During childhood the patient had "black" measles, mumps, chickenpox, smallpox, and scarlet fever. It was stated that she had had typhoid fever at 14 years of age, and dengue fever at 40. Eleven years before the present illness an abscess developed in the right breast following childbirth. Tonsillectomy was done 10 years before, at which time she lost "much blood." All her upper teeth were removed 9 years before.

The patient said she had been "anemic" all her life. About 1916 her blood was reported to show slight anemia. Two years before death she received a series of iron and arsenic injections after which she felt better.

During the winter of 1928 and 1929 she had been as well as usual, but suddenly on the evening of April 14, 1929, she experienced "chills and fever," when she "shook all over." Severe headache accompanied this attack. Her temperature was 101°F. The next day she felt quite well. Similar attacks occurred on April 24, 30, and May 6. The last attack was the most severe, and the headache persisted 4 days. The height of the fever was between 103° and 104°F.

On April 25, 1929, examination of the blood by her physician showed the following: erythrocytes, 3,750,000 per c mm, hemoglobin, 58 per cent, leucocytes, 9,000 per c mm, polymorphonuclear leucocytes, 75 per cent.

On May 1, 1929, the leucocytes were 2,500 per c mm, polymorphonuclear leucocytes, 40 per cent, lymphocytes, 60 per cent.

The patient, on hospital entry, May 11, 1929, appeared well-nourished, and quite comfortable.

Physical examination. There was moderate pallor of the skin and mucous membranes. There was no apparent ulceration of the pharyngeal structures. No enlarged lymph nodes could be felt. The spleen was palpable only on deep inspiration. The liver edge was easily felt.

Laboratory data. Examination of the blood on May 13, 1929, showed erythrocytes, 3,400,000 per c mm, hemoglobin, 76 per cent (S), hematocrit, 45 per cent of cells, leucocytes, 1,200 per c mm, differential count: polymorphonuclear leucocytes, 6 per cent, monocytes, 32 per cent, large lymphocytes, 28 per cent, small lymphocytes, 32 per cent, young lymphocytes, 2 per cent. Several red blood cells showed polychromatophilia and stippling, and there was slight anisocytosis and poikilocytosis. The platelets appeared in normal numbers. There were 12 per cent of reticulocytes.

X-ray examination of the gall bladder failed to reveal stones or any abnormality in the function of this organ. The Wassermann and Kahn tests were negative.

Between May 16 and 29 daily stool examinations were strongly guaiac-positive for blood, but were negative for parasites or ova. Stool cultures were negative for pathogenic bacteria. Several blood cultures showed no bacterial growth.

Examination of the blood on May 20, 1929, showed erythrocytes, 3,450,000, hemoglobin 76 per cent (S), leucocytes, 1,800 cells per c mm, differential count: supravital stain, polymorphonuclear leucocytes, 0, small lymphocytes, 33 per cent, large lymphocytes, 32 per cent, monocytes 35 per cent. The monocytes were sluggishly motile and contained large multilobulated nuclei. Most of these cells were oxidase negative with the peroxidase stain.

The patient gradually grew worse, became comatose and died on May 20, 1929.

Postmortem examination. Autopsy was performed 2½ hours after death. There was a pale yellow tint to the skin and sclerae. The appendix and a few loops of adjacent small intestine were bound together by fibrous tissue. The liver edge projected 11 cms below the tip of the xiphoid and 6 cms below the right costal margin. The mesenteric lymph nodes were not enlarged. Positive findings follow.

Spleen. Weighed 240 grams (about twice normal size). The surface was dark gray-purple and the capsule irregularly thickened. The freshly cut surface was dark red and showed fairly prominent trabeculae. Very little pulp scraped away.

Gastro-intestinal tract. The lower one-third of the esophageal wall and adjacent 2 centimeters of stomach were moderately thickened and the mucosa had a light brown, parboiled appearance. It could be rubbed off with ease. Remaining intestinal tract was negative.

Liver. The liver weighed 2,200 grams. It was normal in shape and consistency. There were numerous fibrous tracts on the upper surface. The freshly cut surface was red-brown with indistinct markings. The gall bladder was thin-walled and contained a small amount of normal appearing bile.

Bone marrow. The bone marrow of the vertebrae and sternum was red in appearance and of normal consistency. In the femur it was red in the upper end and mostly fat tissue in the lower end.

Microscopic examination. The wall was congested with a few small lymphocytic infiltrates. The mesenteric lymph nodes showed a few small foci of fibrous tissue. The spleen showed a few small foci of fibrous tissue. The liver showed a few small foci of fibrous tissue. The stomach showed a few small foci of fibrous tissue. The intestine showed a few small foci of fibrous tissue. The appendix showed a few small foci of fibrous tissue.

and invaded by large numbers of bacteria and fungi. Among the bacteria, cocci and medium-sized bacilli were most numerous. Long, slender, branching forms resembling streptothrix were also present, especially in the deeper portions of the submucosa.

Stomach. A specimen from the cardiac portion of the stomach showed diffuse infiltration with lymphocytes and plasma cells.

Spleen. There was slight increase in connective tissue throughout. A few follicles contained central masses of fibrin. There were several small, round well-encapsulated pink staining masses in which no structure could be made out.

Liver. There was slight lymphocytic infiltration of the portal spaces. There were several small homogeneous pink staining masses similar to those in the spleen.

Bone Marrow. A specimen of bone marrow from the upper third of the right femur showed a slightly increased amount of fat. The cells of the hematopoietic centers were diminished in numbers. No polymorphonuclear leucocytes were to be seen. There were numerous promyelocytes with large single nuclei, and faintly neutrophilic cytoplasm. No definite neutrophilic nor eosinophilic myelocytes could be distinguished. There were normal-appearing foci of erythropoiesis. A fairly good number of megakaryocytes was seen. There was a scattering of lymphocytes and plasma cells.

DISCUSSION

The observation of Schultz¹ in 1922 of a group of patients whose clinical pictures were those of leucopenia associated with sepsis resulted in an attempt at formulation of a new clinical entity. This condition has become known as agranulocytosis, agranulocytic angina, malignant neutropenia, idiopathic neutropenia, and by other descriptive terms. In the past it has been customary to attribute the leucopenia to the infecting process, sepsis, or to "toxins" and most of the cases have been taken from that

point of view. In recent years it has become more and more apparent that the disease may not be an entity as was first supposed but more probably a syndrome. The reason for this change in thought is that the composite clinical picture, which is frequently present, is now known not to be associated with a single or specific type of infectious process, but may be found in the presence of a variety of septic conditions as have been reported by Blumer,⁵ Roberts and Kracke,² Thompson,⁶ Rose and Hauser⁷ and others.

This concept of granulocytopenia occurring as a manifestation of multiple clinical disorders in man is an important one, and has suggested to Rosenthal,⁸ among others, that there may be a leucopenic predisposition or trend in certain individuals. During the life of this patient she was beset with a multiplicity of unrelated types of infection. Terminally there was a profound and persistent idiopathic neutropenia which was found at autopsy to be associated with an esophagitis and gastritis.

The bone marrow in this patient appeared fundamentally different from that in the previous patient. Here there was evidence of adequate platelet and red blood cell production from their precursors in the bone marrow, but it seemed apparent that leucopoiesis was retarded or impaired at the promyelocyte stage.

The recent publication of Jackson⁹ and his associates on the use of a purine nucleotide (nucleotide K-96) for use in cases of malignant neutropenia associated with infection offers some encouragement in the treatment of this disease.

We wish to report a case of neutro-

penia associated with infection in which recovery occurred during the course of administration of nucleotide K-96. No definite conclusions can be drawn as yet with regard to the efficacy of this therapeutic agent until a large number of cases have been studied. The course taken by the leucocytes in the patient reported below is given in figure II.

Case III, Staphylococcus Lymphangitis with Leucopenia, Patient's Subsequent Recovery. S. R. (Hospital No 64,717), a white American housewife, aged 52 years, entered the hospital February 29, 1932. She stated that one week prior to hospital entry she had received a slight burn on the antero-radial aspect of the left wrist. This was followed by scab formation, and so far as she knew, the lesion was healing. The day before entry, the patient noticed for the first time "red streaks" extending up the anterior and medial aspects of the left forearm.

Her past history was unimportant except that in childhood she had mumps, pertussis, and measles. Twenty years ago she had an abscess in the left hand that had promptly healed. During the past year she had been under the care of a physician for arterial hypertension.

Physical examination. The patient was well-nourished and developed. There was no apparent ulceration of the pharyngeal structures. No enlarged superficial lymph nodes could be felt. Neither the spleen nor the liver were found enlarged on palpation. The blood pressure was 170 systolic, and 80 diastolic. There was a small, slightly elevated round, hyperemic lesion on the radial aspect of the left wrist. No purulent material was visible. Extending up the forearm were numerous red and enlarged lymphatic vessels. The patient's temperature was 38.4°C, the respiration rate, 24 per minute, and the pulse beat, 120 per minute.

Laboratory data. Examination of the blood on February 29, 1932, showed erythrocytes 4,600,000, hemoglobin, 85 per cent (S), leucocytes, 8,600 cells per c mm, differential count: polymorphonuclear leucocytes, 78 per cent, polymorphonuclear basophiles, 1 per cent, lymphocytes, 16 per cent, monocytes

5 per cent. The platelets appeared slightly increased in number. Several blood cultures showed no bacterial growth. Cultures obtained on two occasions from the inflammatory process on the left wrist were reported to contain *Staphylococcus aureus*. Soon after entry, the patient's left arm was placed in a hot magnesium sulphate bath for two hours. This procedure was carried out twice daily.

Course of illness. On the third day of the patient's stay in the hospital, her leucocytes were found to number 800 per c mm, and the following day, 400 per c mm. Nucleotide (K-96) in amounts of 10 cc was administered intramuscularly twice daily for 9 days. Beginning about the fifth day after the initial injection of nucleotide, an increase in the number of polymorphonuclear leucocytes became apparent in the peripheral circulation. On the eleventh day of this treatment, the leucocytes were 10,050 per c mm of blood. Coincident with the increase in the number of leucocytes there was a lessening in the severity of the patient's infection. Fifteen days after the patient entered the hospital there was a complete disappearance of the inflammatory process and the patient's temperature had returned to normal. In figure 2 are recorded the temperature and blood counts of the patient together with the time interval during which nucleotide was administered.

Case II - Acute Myeloblastic Leukemia with Chloroma. E. I. M. (Hospital No 59,836), a four-year old white female, was admitted to the Pediatric Service of the University of California Hospital February 18, 1931, because of pallor and weakness of six weeks' duration. In the past she had had pertussis at 2 years of age followed by a severe attack of scarlet fever. This was complicated by otitis media. The patient was a girl previously healthy. In November 1, 1930, when she developed "cold" with severe nasal discharge, the "cold" failed to respond to treatment and about the middle of November the nasal color had become pale. She had become weak and was frequently ill. She had lost weight and bedridden. During the last few days in bed.

*We wish to thank Dr. J. H. H. for his assistance in the preparation of this report.

became noticeable upon exertion. About the middle of January, a swelling of the frontal portion of the skull appeared just above the nose, and both eyes began to appear more prominent than previously. Physical examination on admission disclosed an undernourished, pale child who was obviously ill. There was no evidence of rash or petechiae in the skin. All superficial lymph glands were slightly enlarged, discrete and firm. The anterior fontanel was open and the an-

cent (S), the red blood cells were 840,000 per c mm, and the white blood cells, 1,550 per c mm. In the differential count, using the supravital staining technic, there were polymorphonuclear leucocytes, 31 per cent, large lymphocytes, 12 per cent, small lymphocytes, 16 per cent, myelocytes, A, 1 per cent, B, 5 per cent, C, 25 per cent, monocytes, 10 per cent. Tests for bleeding time and clotting time showed these functions to be within normal limits. The blood Wasser-

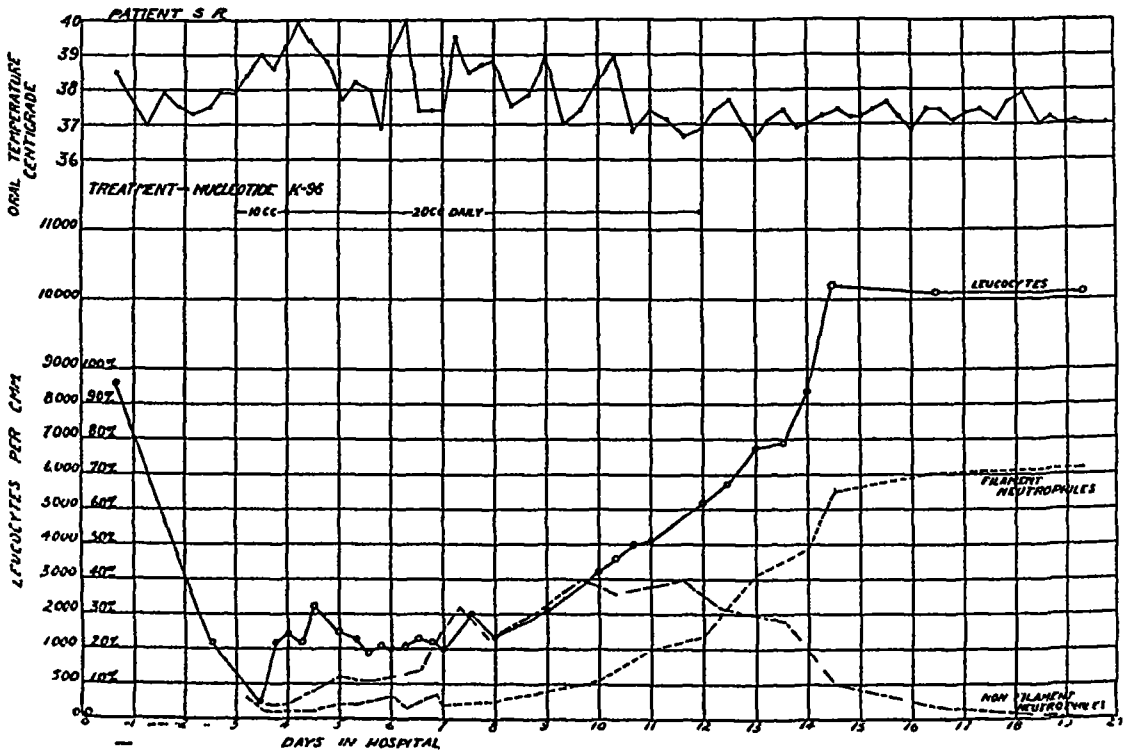


FIG 2 The occurrence of leucopenia in a female patient with lymphangitis of the arm followed by recovery during the intramuscular administration of nucleotide K-96

terior sutures were separated. The forehead, just above the bridge of the nose, bulged over an area of about 3 by 3 inches, and the veins in this area were slightly more prominent. A loud bruit, synchronous with the pulsation of the temporal artery, was heard over this area. There was bilateral exophthalmos, most marked on the right. Ophthalmoscopic examination showed bilateral choked discs of 1 to 1½ diopters. There were a few scattered retinal hemorrhages of small size. The heart and lungs were normal. The liver edge was felt 2 cms below the right costal margin, and the spleen was felt 3 cms below the left costal margin. The laboratory data showed a hemoglobin of less than 20 per

cent. The mann reaction was one plus. X-ray examinations of the long bones and ribs were negative and there was no evidence of bony destruction in the skull, but there were signs of increased intracranial pressure. Blood cultures failed to produce any bacterial growth.

Course of illness. Following exposure to the x-ray on five different occasions, the mass in the frontal region of the skull diminished in size and the exophthalmos receded. Her strength and appearance were improved by six transfusions of whole blood in amounts of 300 cc. On March 22, 1931, a few days after the last x-ray treatment, a fever of 40°C was noted, and petechial

hemorrhages developed over the forehead, nose and upper chest. From this time on the patient failed to improve following transfusion. A grayish necrotic patch appeared on the right tonsil two weeks before death, and one week later there was evidence of bronchopneumonia. She lost strength rapidly, and on April 16, 1931, death occurred.

The gross findings at the autopsy performed by Doctor Charles L. Connor showed numerous varying-sized hemorrhages in all the serous coverings of the body cavities. The lymph nodes were but slightly enlarged and everywhere were firm and discrete. The liver was firm and slightly enlarged. It weighed 600 grams. The spleen was large and weighed 100 grams. Both kidneys were larger than normal and contained numerous minute pale green areas. The lungs showed no evidence of pneumonia, but there were many small subpleural hemorrhages. In the anterior cranial cavity beneath the dura on both sides lateral to the midline there were deposits of greenish material resembling old hemorrhage, and there were some recent bright hemorrhagic spots also present. The layers of the dura, particularly along the longitudinal sinus and around the lateral and

straight sinuses were infiltrated with a greenish, cellular substance which appeared to be tumor. A small mass of similar material projected through the cribriform plate into the nasopharynx. The bone marrow in the upper third of the right femur appeared light red in color, cellular and seemed to contain very little fat.

On microscopic examination of the bone marrow, it was observed that there was an almost complete absence of fat, and that the normal architecture was in a large measure replaced by masses of cells. These cells contained large, clear, rounded nuclei with the chromatin clustered about the nuclear membrane, as seen in figure 3. The cells appeared immature and many contained an indented bay in the nucleus. None contained granules in the cytoplasm. This cell was considered a myeloblast rather than the so-called lymphoblast. Mitoses were frequently seen. There were very few polymorphonuclear leucocytes, but moderate numbers of myelocytes were discovered. Very small islands of erythroblastic tissue were seen, and rarely a megakaryocyte. Examination of the heart, lungs, liver, spleen, kidneys, adrenals, ovaries, and lymph nodes showed areas of infil-

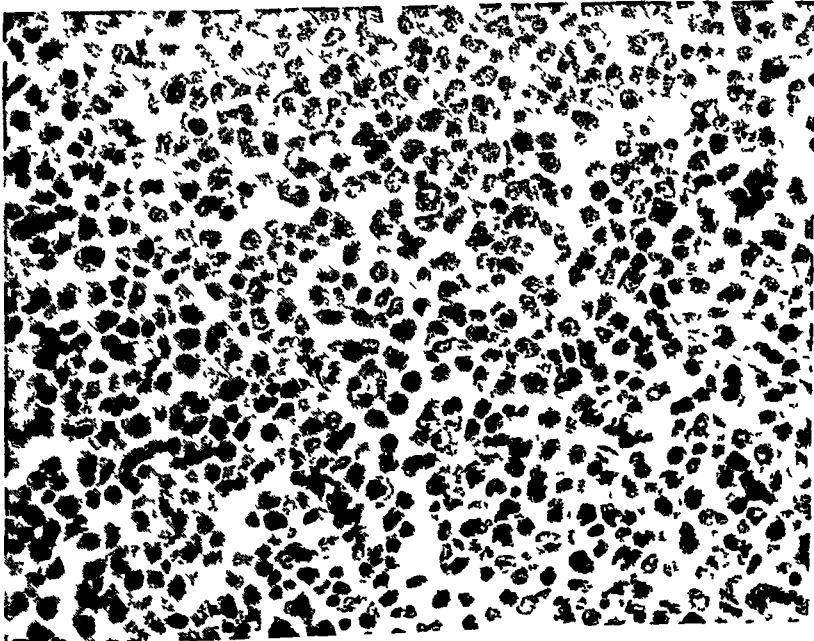


FIG 3 Specimen of bone marrow removed from sternum of patient in case III. Note marked hyperplasia and presence of large numbers of immature leucocytes.

tration with cells resembling those described above. The tumor tissue removed from the dura was made up largely of this immature cell. It was believed that the concentration of the immature cells, as has been shown by Mallory, accounted for the pale green chloromatous color.

COMMENT

This, then, is another case of idiopathic neutropenia, the pathologic physiology of which apparently is entirely different from the two preceding cases. In contrast to cases I and II, there was in case IV increased cellularity of the bone marrow (figure 3) consisting almost entirely of leukoblastic tissue. Another patient, a female 56 years of age, presented a picture of the bone marrow similar to this in which active maturation of the leucocyte seemed retarded at the myeloblast stage.

Of rather rare occurrence is the development of severe leucopenia in conditions characterized by hemorrhagic tendencies, and in which abnormalities in platelet production appear fundamental. Minot¹⁰ has reported such an instance in association with thrombocytopenic purpura hemorrhagica.

It is of course well known that severe leucopenia may also develop in association with certain abnormalities in red blood cell production. In patients with pernicious anemia, in relapse, leucopenia is more often present than absent. The occurrence of leucopenia in patients with sprue and Banti's disease are other examples. Two instances of leucopenia occurring in patients with severe anemia diagnosed as acquired hemolytic icterus may be briefly cited as follows.

Case I. An Italian male, 58 years of age, had been in good health prior to June, 1930,

when he began to notice the gradual onset of a yellowish tinge in the whites of his eyes. In February, 1931, his skin appeared icteric and his sclerae were yellow in color. His hemoglobin was 40 per cent (S), the red blood cells numbered 2,130,000 per c mm and the white blood cells were 2,900 per c mm. The blood platelets were slightly reduced in number, and 10 per cent of the nucleated cells in the stained blood smear were normoblasts. There was slightly increased hemolysis of the red blood cells to hypotonic salt solution. It is now one year after splenectomy and the patient appears in good health, he has a slight "secondary" anemia, but the leucocytes are present in normal numbers.

The illness from which the second patient suffered is not so clearly defined.

Case VI. This patient was a white male, 72 years of age, who had noticed increasing pallor and weakness of 3½ years' duration. During the past year his family physician had given him several transfusions of blood. When he entered the hospital, slight icterus of the sclerae was noted, and the spleen was moderately enlarged. His hemoglobin was 26 per cent (S), there were 1,160,000 red blood cells per c mm, and the leucocytes were 2,300 per c mm. The platelets were slightly reduced. The icterus index was 15. Reticulocyte counts made daily showed the presence of from 6 to 10 per cent of these cells. Analysis of the gastric content showed the presence of free hydrochloric acid. A biopsy of the sternal marrow was performed and the specimen of tissue removed was extremely cellular and made up almost entirely of normoblasts (figure 4). Because of the foregoing data and the failure to attribute the anemia to blood loss, pernicious anemia or tumor, acquired hemolytic icterus was considered the most likely diagnosis. Splenectomy was resorted to as a therapeutic agent. Two days after the operation the patient died following paralytic ileus. The report from the pathology laboratory was splenomegaly, "type compatible with hemolytic icterus." A postmortem examination revealed the presence of marked erythro-

blastic and normoblastic hyperplasia of the bone marrow, but otherwise was essentially negative

These cases, then, illustrate different types of neutropenia of obscure origin and represent different types of bone marrow reaction leading to alteration in leucopoiesis

BENIGN LEUCOPENIA OF OBSCURE ORIGIN

In group V of table I have been placed the number of patients in whom leucopenia was reported present but in whose records either no diagnosis appears or one that may be considered *functional in nature*. This group comprised 114 of the cases of leucopenia, or 97 per cent of the total. In this group appear the patients whose complaints were those of chronic fatigue, lassitude, lack of appetite, and vague sorts of distress of one sort or another. Among such cases some of the diag-

noses were listed as neurasthenia, psychosis, hysteria and the various neuroses. Reference to similar cases have been made by Cabot,¹¹ Clough,¹² and Roberts and Kracke² who speak of them as states of "debility" associated with leucopenia. Disturbances in endocrine function¹³ and a constitutional factor¹⁴ have also been pointed out as having some possible relationship to decreased leucocyte formation. In this latter group the cause of the leucopenia must be considered intrinsic in character and decidedly obscure in origin.

SUMMARY AND CONCLUSIONS

1 Five cases of severe leucopenia of obscure origin are presented. Attention is called to the different types of bone marrow reaction occurring in the various cases, namely, aplasia of the bone marrow, depression of leucopoiesis only, hyperplasia of the leuko-

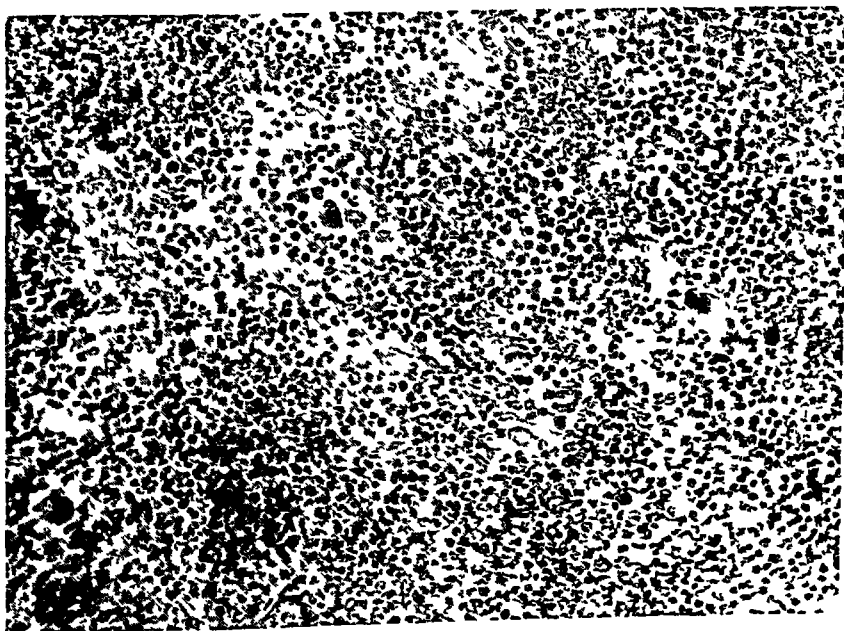


FIG 4 Specimen of bone marrow removed at biopsy from sternum of patient in case VI. Note marked normoblastic hyperplasia.

poietic tissue, and hyperplasia of the erythropoietic tissue

2 A case of leucopenia associated with lymphangitis of the arm in an adult female is reported in which recovery occurred during the course of administration of nucleotide K-96

3 Among the 10,000 case records of patients cared for in the University of California Hospital between 1920 and 1931, inclusive, examination of the blood revealed leucopenia in 1,167 or 11.67 per cent of the cases

4 611 of the 10,000, or 52.4 per

cent of the cases of leucopenia, occurred in females and 556, or 47.6 per cent, occurred in males. Thus, leucopenia was slightly more prevalent in females than males

5 Leucopenia occurred frequently as a mild manifestation in patients with vague symptoms of one sort or another, such as chronic fatigue, 9.7 per cent of the cases of leucopenia were classified, therefore, as benign leucopenia of obscure origin

6 A table of the frequency incidence of leucopenia is given

REFERENCES

- ¹DOAN, C. A., CUNNINGHAM, R. S., and SABIN, F. R. Experimental studies on the origin and maturation of avian and mammalian red blood cells, *Contrib Embryol. Carnegie Inst., Wash.*, 1925, **xvi**, 163-226
- ²ROBERTS, S. R., and KRACKE, R. R. Agranulocytosis, its classification, cases and comments illustrating granulopenic trend from 8,000 blood counts in the South, *ANN INT MED*, 1931, **v**, 40-51
- ³MILIS, E. S. Idiopathic aplastic anemia or aleukia hemorrhagica, *Am Jr Med Sci*, 1931, **clxxxi**, 521-533
- ⁴SCHULTZ, W. Über eigenartige Halserkrankungen (a) Monozytenangina, (b) Gangraneszierende Prozesse und Defekt des Granulozytensystems, *Deutsch med Wchnschr*, 1922, **xlviii**, 1495-1496
- ⁵BILMÉR, G. Agranulocytic blood picture in conditions other than angina, *Am Jr Med Sci*, 1930, **clxxix**, 11-16
- ⁶THOMPSON, W. P. Abnormalities in the white blood cell response, leukoid, atypical leukemic and leukopenic blood pictures, *Am Jr Med Sci*, 1931, **clxxxi**, 334-352
- ⁷ROSE, L., and HAUSER, K. M. The identity of the so-called agranulocytic angina: report of case, *Arch Int Med*, 1929, **xlii**, 533-548
- ⁸ROSENTHAL, N. Hematological aspects of agranulocytosis and other diseases accompanied by extreme leukopenia, *Am Jr Clin Path*, 1931, **i**, 7-32
- ⁹JACKSON, H. JR., PARKER, F. JR., RINEHART, J. F., and TAYLOR, F. H. L. Studies of the diseases of the lymphoid and myeloid tissues, VI. The treatment of malignant neutropenia with pentose nucleotides, *Am Jr Med Assoc*, 1931, **xcvii**, 1436-1440
- ¹⁰MINOT, G. R. Diminished blood platelets and marrow insufficiency, a classification and differential diagnosis of purpura hemorrhagica, aplastic anemia and allied conditions, *Arch Int Med*, 1917, **xix**, 1062
- ¹¹CABOT, R. C. A guide to the clinical examination of the blood for diagnostic purposes, 1909, William Wood & Co., New York, 106
- ¹²CLOUGH, P. W. Diseases of the blood, 1929, Harper & Brothers, New York, 63
- ¹³FRIDEMANN, U. Angina agranulocytotica, *Ztschr f klin Med*, 1928, **cvi**, 54-66
- ¹⁴BAUER, J. Die konstitutionelle Disposition zu inneren Krankheiten, 1924, J. Springer, Berlin

A Clinical Study of the Graves' Constitution and Its Relation to Thyroid Disease

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IT is not the purpose of this paper to discuss the relative merits of existing conceptions of thyroid disease nor to add to such theories, but to present certain data—gathered and interpreted by the clinician—bearing on the constitutional background of hyperthyroidism as expounded by Warthin. From time to time mention has been made of the frequent association between thymic enlargement and thyroid disease, but Warthin's address entitled "The Constitutional Entity of Exophthalmic Goiter and So-Called Toxic Adenoma"¹ is the most comprehensive statement of the significance of this association and has given rise to the phrase "Graves' Constitution (Warthin)" which has been used by other writers to designate this concept. It would be out of place to review that address in this paper, but a brief statement of the essential features is necessary for clarity.

The clinical syndromes, variously spoken of as hyperthyroidism, toxic goiter, toxic adenoma, Graves' disease, and exophthalmic goiter, are well known to physicians generally. Since the time of Parry, Graves and von Basedow, the original triad of goiter,

exophthalmos and tachycardia has been expanded by the addition of symptoms and signs referable to practically every organ in the body. Recent investigations have cast doubt on the assumption that thyroid dysfunction is the primary factor in this condition. The very multiplicity of names which has grown up to designate variations from the typical picture bears testimony to the complexity of the present conception and the difficulty of classifying cases seen. Warthin contends that there is, however, one underlying factor common to all who have this disease syndrome, and that factor is a constitutional abnormality, to which he has applied the term *Graves' constitution*.

The general appearance of the individual with this symptom complex is often so striking that the condition is recognized at a glance by even a relatively inexperienced observer. Quoting from Warthin¹ it is "expressed in *juvenile morphology* and rapid functional reaction." The essential anatomic stigmata, as seen at the autopsy table, are perhaps less widely recognized. Grossly there is found a persistent hyperplastic thymus. The importance and constancy of this finding was emphasized by Potter² in a review of twenty-two autopsies on cases of

¹From the Department of Internal Medicine of the University of Michigan. Received for publication, March 2, 1932.

exophthalmic goiter, and more recently by Moschcowitz,³ who, while not finding it in all instances, reports it in ninety-five per cent of his fatal cases. Of equal importance is a generalized hyperplasia of the lymphoid tissue throughout the body, including not only the lymph nodes but also Peyer's patches in the intestine and the minute islands of lymphoid tissue which are found scattered throughout the body. Scarcely less striking is the underdevelopment of the vascular system, particularly the heart and aorta. Likewise the hypoplasia of the adrenals, especially of the medullary portion, is of diagnostic and perhaps also of functional significance.

The lymphoid hyperplasia is the anatomical feature of diagnostic significance in the microscopic examination of the excised thyroid gland. The normal thyroid shows no lymphoid follicles, but there are scattered through it primitive lymph nodes, perhaps represented by only a few lymphoid cells, and so small as to be difficult of recognition. In the Graves' constitution these primitive nodes become hyperplastic, with the development of germinal centers. While this has been recognized by many writers, few have laid stress upon it, but Warthin^{1, 4} has amply demonstrated its diagnostic significance as indicating Graves' constitution. He maintains that every case of exophthalmic goiter, hyperthyroidism, toxic goiter, toxic adenoma, or other variation of the clinical syndrome will show in the excised thyroid gland this evidence of a constitutional abnormality. He does not hold, however, that every person with Graves' constitution will show this clinical syn-

drome. While the individual with this constitutional abnormality is always potentially a subject for so-called thyroid disease, the condition may be dormant throughout his lifetime. We do not know what influences bring out the clinical syndrome. Consequently a simple goiter, a simple adenoma, an otherwise apparently normal thyroid, or even a thyroid of below normal function, may or may not belong to the Graves' constitution. An outline intended to clarify this relationship is given below in table I.

TABLE I

GRAVES' CONSTITUTION

(Lymphoid hyperplasia in thyroid)

Definite thyroid disease

- (a) Exophthalmic goiter
- (b) Toxic goiter, hyperthyroidism and other less well defined abnormalities
- (c) Toxic adenoma

Thyroid function normal or decreased

(Thyroid disease always potentially present, however)

- (a) Normal size and otherwise structurally normal thyroid
- (b) Diffuse colloid goiter
- (c) Adenomatous goiter without toxicity

NO EVIDENCE OF GRAVES' CONSTITUTION

(Thyroid function normal or reduced)

- (a) Normal thyroids
- (b) Diffuse colloid goiter
- (c) Adenomatous goiter

This constitutional relationship to thyroid disease has been discussed at length in three papers appearing since Warthin's address. Simpson,⁵ analyzing the cases at the Miami Valley Hospital corroborates Warthin's findings in their entirety. Hellwig⁶ in a discussion based on fifty-four excised glands and six autopsies disagrees throughout with Warthin's conception. Quite aside from the meager extent of his

material, he has completely misinterpreted Warthin's idea of the Graves' constitution. He implies that since he found lymphocytic hyperplasia in 38.5 per cent of the cases showing no hyperthyroid symptoms there can be nothing diagnostic in this finding. As already pointed out, Warthin contends that Graves' constitution may be present in an otherwise normal thyroid, and that if the stimulus, concerning which we admittedly know little, is not present to set off the metabolic disturbance, the hyperthyroid symptoms may remain latent throughout the individual's lifetime.

A very interesting hypothesis has been advanced by Moschcowitz.³ As already mentioned, he notes an almost uniform association of the thymico-lymphatic constitution with exophthalmic goiter. He maintains, however, that the constitutional background is a neuro-psychiatric instability, which he holds is most often seen in individuals of the thymico-lymphatic habitus, or to use Warthin's nomenclature, the Graves' constitution. He thus believes that there is an indirect relationship between the Graves' constitution and exophthalmic goiter, differing from Warthin, who believes that the neuro-psychiatric instability is merely an attribute of the constitution, and that the constitution is the fundamental requisite for thyroid disease.

In view of the conflicting ideas, I have attempted an evaluation of the importance of the Graves' constitution, approaching the problem as a clinician. In order to limit the amount of material, the period 1927 to 1930 was selected and all the cases were included which, during that period, had been

studied on the medical service of the University of Michigan Hospital and subsequently transferred to the surgical service for thyroidectomy. The excised glands were all examined in the Department of Pathology of the University of Michigan, of which Dr Warthin was at that time the director. The clinical records were thoroughly studied, including laboratory data, such as determinations of basal metabolic rate, and the case was evaluated clinically before any reference was made to the pathologist's report. The clinical and pathological findings were then tabulated and compared. A series of 245 cases was studied and the results are presented in table II. For the sake of clarity, I have avoided fine clinical differentiations, placing together in one group those conditions referred to as hyperthyroidism, exophthalmic goiter without eye signs, toxic goiter, etc.

DISCUSSION

It will be seen at once that 90 per cent of the cases fall into Warthin's classification in just the manner which would be expected. The other 10 per cent in which there is an apparent disagreement between clinical findings and the pathological diagnosis calls for further study. I shall refrain as far as possible from theoretical conclusions, since a presentation of the facts concerning individual cases seems more to the point. For the sake of brevity the cases have been grouped in the above table and numbered with Roman numerals and these numbers will be used to identify them in the following discussion.

The four cases in group I, which clinically were typical exophthalmic

TABLE II

CLINICAL DIAGNOSIS	PATHOLOGICAL DIAGNOSIS			PERCENTAGE AGREEMENT
Group I	Exophthalmic goiter	Exophthalmic goiter with adenomas	No evidence of Graves' constitution	
Exophthalmic goiter with eye signs 67 cases	58 cases	5 cases	4 cases	93.9%
Group II Exophthalmic goiter without eye signs, hyperthyroidism, etc 71 cases	Exophthalmic goiter, or Graves' constitution 53 cases	14 cases	4 cases	94.4%
Group III Toxic adenoma 3 cases	3 cases			100%
Total 141 cases	114 cases	19 cases	8 cases	94.3%
Group IV Toxic adenoma 66 cases	Adenomatous goiter with Graves' constitution 48 cases	No evidence of Graves' constitution 18 cases		72.7%
Group V Non-toxic adenoma 38 cases	12 cases	26 cases		100%
	Percentage of non-toxic adenoma showing no evidence of Graves' constitution 68.4%			
Total cases 104	Agreement 86 cases	Disagreement 18 cases		82.7%
Grand Total 245 cases	Agreement 219 cases	Disagreement 26 cases		89.3%

goiter and pathologically showed no evidence of Graves' constitution, are perhaps the most significant. One of these four cases was known to have taken iodine for at least two months previous to operation and another stated that he had taken two or three kinds of goiter medicine before admission. In both these instances the pathologist stated that the microscopic appearance of the thyroid was that usually associated with excess use of iodine. The opinion has frequently

been advanced that overuse of iodine may induce toxicity in an otherwise normal thyroid, an assertion which it is not within the scope of this paper to defend or contest. It was practically impossible to form any opinion concerning the rôle of iodine before admission in the cases reviewed in this study. The prevalence of iodine-containing nostrums posing as "goiter cures" and the frequency with which the patient has no idea of the character of medicine given him by his physi-

cians renders a clinical history of the amount of iodine taken extremely unreliable. While I make no attempt to explain the discrepancy in these two cases by the history of use of iodine the possibility exists that it is a factor.

A third case not showing the histological criteria of Graves' constitution is in some respects not entirely typical of exophthalmic goiter. There was a history of 35 lbs weight loss with a good appetite. Physical examination showed a warm, moist skin and marked exophthalmos. On the other hand, the heart rate was only 65 and the basal metabolism was variable, down to plus 21 per cent at one determination and up to plus 38 per cent four days later. Eight determinations were made showing this type of fluctuation and there was no drop in the basal rate following the use of Lugol's solution. While it seemed that this case must be included in the group of exophthalmic goiters, the diagnosis might be questioned by some. In the fourth case, however, there seems to be no question of the clinical diagnosis, the case being typical throughout of exophthalmic goiter, and the pathological examination of an adequate amount of material showed nothing indicating Graves' constitution.

In group II the diagnosis was open to dispute in one case listed as exophthalmic goiter without exophthalmos because of the presence of diabetes mellitus. The symptoms were those of the diabetes and the diagnosis of hyperthyroidism was based largely on a basal metabolic rate of plus 33 per cent dropping to plus 15 per cent after the use of Lugol's solution. In a second case similarly classified the out-

standing features were 17 pounds weight loss with an appetite described as only fair, a pulse of 100, and a basal metabolic rate of plus 28 per cent dropping to plus 18 per cent on bed rest alone. While the picture suggests a so-called "mild hyperthyroidism" the array of clinical data is not entirely convincing. A third case is similar to this, weight loss of 20 pounds, fatigue, pulse 92, and a basal metabolic rate of plus 23 per cent dropping to 8 per cent without medication. The fourth case of non-agreement between clinical picture and the pathological criteria of Graves' constitution is quite typical of "exophthalmic goiter without exophthalmos", but the patient was 4 to 5 months pregnant. Whether this complicating factor disturbed the general picture is difficult to determine.

From this further study of these eight cases of discrepancy it will be seen that in one instance there is an apparent sharp departure from Warthin's conception of "thyroid disease" and the Graves' constitution. In the other seven cases the degree of divergence from this conception is more or less striking. While there is no attempt in this paper to explain away discrepancies and reconcile conflicting data, one other fact should be presented for the sake of fair consideration of the data. While several blocks were selected from each thyroid for microscopic examination, serial sections were not run. It has been demonstrated that in Graves' constitution the distribution of the lymphoid tissue is not uniform. It is entirely possible that some thyroids reported as not belonging to Graves' constitution may have contained lymphoid tissue which

was not present in the sections examined. Every clinician is familiar with the case of cancer or tuberculosis which is not diagnosed on biopsy because the diagnostic tissue was not present in what was excised for examination, and it is possible that Graves' constitution was not found in some of these cases because of an analogous situation.

In the group of the adenomatous goiters (group IV in table II) there are 18 cases which clinically would be considered "toxic adenoma", but in which the pathologist reported "no evidence of Graves' constitution". In this group evaluation of the data is more difficult, both from the clinical and the pathological points of view. As is well known, the clinical syndromes in this group are less well defined than in the case of "exophthalmic goiter", and it is sometimes difficult to say whether a case should be classified as "simple adenoma" or "toxic adenoma". On the other hand, the pathologist is handicapped because the excised material often consists almost entirely of adenoma, and frequently an adenoma shows no evidence of Graves' constitution whereas the surrounding thyroid tissue shows the stigmata. Thus one of the 18 cases, clinically toxic and pathologically not of Graves' constitution, showed practically nothing in the excised tissue except a very large adenoma. It would be impossible to state what might have been found in the thyroid tissue very properly left behind or in that surrounding the adenoma which had undergone a complete pressure atrophy.

The effect of congestive heart failure

in confusing the clinical appearance of the case of adenomatous goiter is also generally recognized. Five cases were characterized by heart failure which dominated the clinical picture. The basal metabolic rate was definitely elevated in all these instances, but the diagnosis was not as clear-cut as might be desired.

Two other instances are worthy of special mention. One patient had diabetes mellitus. The basal rate was moderately elevated, plus 28 per cent on two occasions falling to plus 15 per cent before operation. The second case record contains a note to the effect that while the basal metabolic rate was definitely elevated, the patient at no time appeared toxic, nor did he have the classic physical signs of "toxic adenoma". None of these cases showed the pathological signs of Graves' constitution.

Regardless of whether the clinical diagnosis is discounted in the seven cases and the pathological opinion in the eighth there still remain ten cases in which it seems that no clinical diagnosis except "toxic adenoma" is possible, in which the excised material was adequate for microscopic examination and in which the pathological diagnosis was "no evidence of Graves' constitution". In group V, the non-toxic adenoma, as already explained, there are no discrepancies to be discussed. Those belonging to Graves' constitution are considered as potentially toxic, but may not have developed any toxic symptoms.

It has become proverbial that statistics can be made to prove or disprove almost any conclusion. Too often the writer approaches his problem with a

preconceived idea of what he wants to prove and naturally he is attracted by facts which appear to substantiate his views. Because of the fact that the very mass of material would make impossible individual consideration of cases, I have made no attempt to gather an imposing array of material. In order that clinical judgment should be uninfluenced by pathological findings, I have utilized the simple device of forming my clinical impression before reading the pathologist's report. I have not disregarded the recorded clinical diagnosis, but because of the fact that it is recorded *after* reading the pathologist's report and accordingly is probably influenced by that report, I have also considered all the other clinical data such as history, physical examination and ward notes. Finally in those instances where the diagnosis seemed open to question, I have given the salient features of the case record. It is my hope that this clinically interpreted data will be of more value than a simple comparison of recorded diagnoses. Using this approach it is apparent that in 245 cases of thyroid disease studied, 89.4 per cent of the clinical diagnoses were in agreement with Warthin's conception of the Graves' constitution as a fundamental factor in these disturbances, the pathological examination of the excised thyroid gland being the criterion of the existence or non-existence of the constitution. In the remaining 10 per cent the clinical diagnosis may be considered open to question in certain instances, but on the basis of the information available it must be said that these cases do not substantiate Warthin's premise.

CONCLUSIONS

It is not within the scope of this paper to explain why the comparison of clinical and pathological findings does not reach 100 per cent of agreement. I have suggested certain possibilities which may explain some instances of discrepancy, but these are impossible of proof with data at hand. I do not wish to be either defendant of, or apologist for, the view presented by Warthin. However, the occurrence of a specific constitutional type in nine out of ten instances of this metabolic disturbance cannot be without significance. I do not feel that my statistics establish beyond question that Graves' constitution is necessary to the development of exophthalmic goiter or the so-called toxic adenoma. They do, however, indicate that these conditions usually develop in the individual with this constitutional anomaly. It has not been my purpose to emphasize a new diagnostic criterion for the pathologist. The conception of the Graves' constitution as presented by Warthin is far more than that. It is, in fact, fundamental in the pathogenesis of thyroid disease and has bearing on the rationale of treatment. My findings, in the main, support Warthin's view, and it is my hope that there may be studies from other sources which will further clarify the situation, either by addition of further support or by refutation of this conception.

SUMMARY

1 Graves' constitution was described by Warthin and others as a congenital body type always present in the clinical syndromes of Graves' dis-

ease, hyperthyroidism, and toxic adenoma

2 A group of cases, from which the thyroid gland was pathologically examined following operation, has been clinically interpreted and studied

3 Of 245 cases thus studied 219, or 89.4 per cent, were in clinical agreement with Warthin's conception. In 141 cases of exophthalmic goiter, the agreement was 94.3 per cent, in 104 cases of adenomatous goiter, the agreement was 82.7 per cent

4 In view of these findings, Warthin's conception of the Graves' constitution appears as an important contribution toward a more complete

understanding of thyroid disease. The initiating factor of the thyrotoxic symptoms is not clear and many phases of the subject are still obscure, but it seems evident that a constitutional anomaly, present from birth, is a factor of great importance.

I wish to acknowledge my great indebtedness to the late Dr A. S. Warthin for stimulation to undertake this problem, and for encouragement to carry it through to the end. I also wish to give recognition to Dr C. V. Weller, Professor of Pathology and Director of the Pathological Laboratories of the University of Michigan, for his assistance in the evaluation of the pathological material in the cases used as a basis for this report.

REFERENCES

- ¹WARTHIN, A. S. The constitutional entity of exophthalmic goiter and so-called toxic adenoma, *Ann Int Med*, 1928, 11, 553-570
- ²PORTER, E. B. Persistent thymus in exophthalmic goiter, in *Contributions to Medical Science: The Aldred Scott Warthin Anniversary Volume*, George Wahr, Ann Arbor, 1927, pp. 205-220
- ³MOSCHCOWITZ, E. I. The nature of Graves' disease, *Arch Int Med*, 1930, xli, 610-629
- ⁴WARTHIN, A. S. The pathology of goiter, *Proc Inter-State Postgrad Med Assoc of N Am*, 1929, 383-385
- ⁵SIMPSON, W. M. Graves' constitution (Warthin), *Am Jr Surg*, 1929, vii, 22-26
- ⁶HELLWIG, C. A. Graves' constitution (Warthin), *Surg, Gyn and Obs*, 1931, lxi, 43-57

Photosensitization

By HAROLD F. BLUM, Ph D, *Berkeley, California*

THERE are phenomena in a considerable number which are produced in living systems by substances not normally present in these systems which sensitize them to light. These phenomena are described collectively under the term *photodynamic action*, they are of widespread occurrence and manifest themselves in various ways. As examples may be cited the hemolysis of red cells and the destruction of bacteria by light and eosin, and the poisoning of domestic animals by substances ingested from buckwheat. As has been pointed out by Blum (1932), these phenomena are apparently based upon similar chemical reactions, since, so far as they have been studied, all require the presence of molecular oxygen. This separates them at once from a number of similar phenomena produced by ultraviolet light without sensitizers, which take place in either the presence or absence of oxygen. It will be the purpose of the present communication to consider the possible relationship of such mechanisms to clinical medicine.

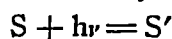
We will consider first the relation-

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ship of such mechanisms to certain disease entities, known principally to the dermatologist, which may be classed under the term "light sensitivity." Diseases falling under this head which have been suggested as due to photodynamic sensitization are *Hydroa aestivale seu vacciniiforme*, *Xeroderma pigmentosum*, *Eczema solare*, and others. *Hydroa*, at least, has been widely accepted as a photodynamic phenomenon in which *hematoporphyrin* acts as the sensitizer. I shall not attempt to discuss any of these diseases from a symptomatic standpoint, but only to consider the possibility of abnormal photosensitizers as etiological factors in such conditions.

Before proceeding further, it will be useful to consider a few fundamental principles of photochemistry and of the physiological action of light. Any primary photochemical reaction is assumed to follow the Stark-Einstein equivalence law, according to which a molecule absorbs a quantum of light energy and becomes an activated molecule which persists in the activated state for an extremely short time. This may be represented by the equation



Where S is the light-absorbing molecule, $h\nu$ the light quantum and S' the activated molecule. The molecule S can only absorb light of certain

wave lengths so that only specific wave lengths can activate it. During the short period of activation the molecule may react chemically with other molecules, or undergo other fates which need not concern us here. If a chemical reaction takes place, the type of reaction which occurs will depend not only upon the kind of activated molecule but upon the kind and number of other molecules in the system with which the activated molecule may come in contact. Thus the reaction which takes place depends not only upon the photochemically active molecule and the light which it absorbs, but also upon the other components of the reacting system.

In the human organism there are present certain mechanisms which are stimulated by light. We may assume that the light is absorbed by certain photoactive substances which initiate these reactions, and thus the reactions

are produced only by light of definite wave lengths which are absorbed by this substance. The activating radiations must all lie within the absorption spectrum of the photoactive substance, although all the wave lengths absorbed need not produce the photochemical reaction. The mechanisms of this type which are definitely known in the normal human body are (a) pigmentation of the skin, (b) erythema, and (c) the calcium-phosphorus balance. The wave lengths bringing about these reactions are all in the ultraviolet region, below about $350\text{ m}\mu$ (see figure 1). These reactions may be quite complex in their nature, the calcium-phosphorus balance mechanism is probably due to chemical changes brought about in ergosterol or similar substances circulating in the blood, but the other mechanisms are not so simply explainable. Now it is possible that an upset at any point in one of these

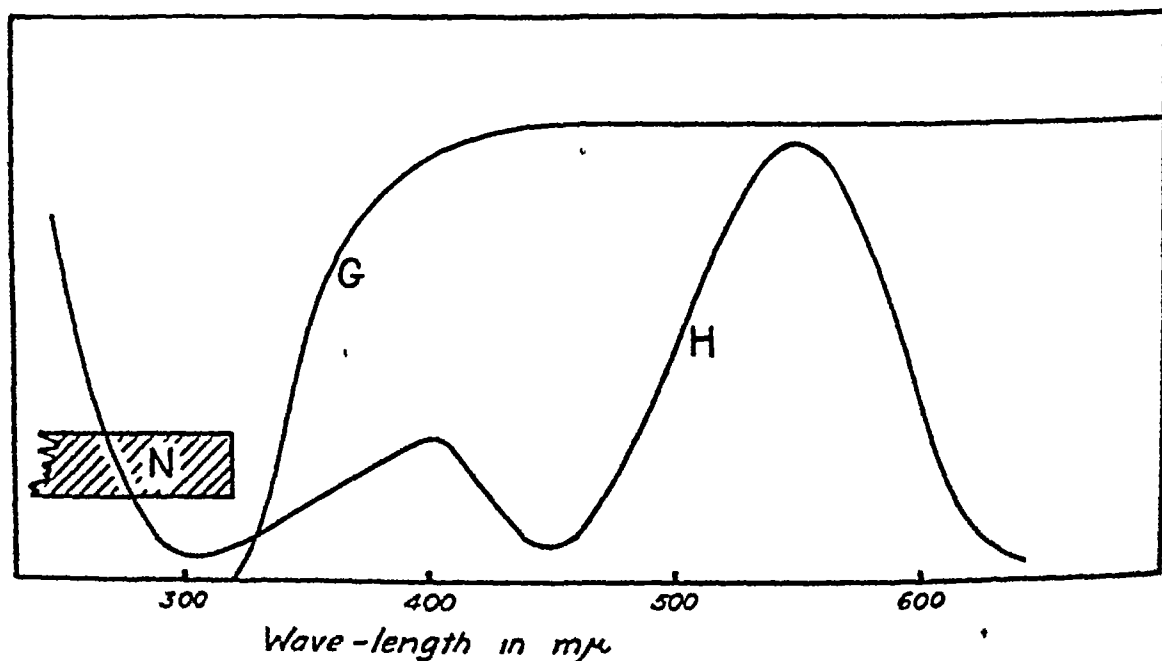


FIG. 1. H = approximate absorption curve of hematoporphyrin, showing position of absorption maxima at $400\text{ m}\mu$ and $560\text{ m}\mu$; only the general regions of absorption are shown. (Actually the curve is much more complex.) N = region of wave lengths producing normal skin reactions. G = lower limit of transmission of window glass.

mechanisms might result in a hypersensitivity of the organism to light, expressed in terms of that mechanism. Thus, for example, it may be that *Xeroderma pigmentosum* is due to an upset in some part of the pigment forming mechanism which does not involve the primary photochemical reaction in any way. In such case the light sensitivity would be brought about by the same rays which bring about the normal pigmentation reaction in the organism.

On the other hand, we have the possibility that light sensitivity may be brought about by abnormally present photoactive substances. Sensitization by such substances might be expected to bring about totally different reactions from those due to the photosensitive mechanisms normally extant in the body, although we cannot neglect the possibility that such abnormal photoactive substances might sensitize the normally existing mechanisms and thus exaggerate these reactions. In either case, the wave lengths bringing about these photochemical reactions would be specific for the abnormally present photoactive substance and must lie within the absorption spectrum of that substance. This should provide us with a possible means of distinguishing between the two alternative mechanisms for the light sensitivity mentioned above, on the basis of the wave lengths of light which are active in bringing about these responses, except in the event that the absorption spectrum of the abnormal sensitizer should correspond approximately with that of the photosensitive substances producing the normal light reactions. In other words, if we find

that wave lengths other than those bringing about the normal reactions of the body to light (around 350 m μ), bring about reactions in the skin or elsewhere, we are probably justified in assuming the presence of an abnormal sensitizer.

Hydroa aestivale seu vacciniforme, a condition in which vacciniform lesions of the skin appear, usually occurs during the sunny period of the year, and is considered generally to be a condition of light sensitivity. Furthermore, the condition is quite generally stated to be due to the photosensitizing action of the abnormal blood pigment, *hematoporphyrin*. As a matter of fact, hematoporphyrin is not actually a naturally occurring pigment, but is a substance produced in the laboratory from hemoglobin. The naturally occurring pigments are uroporphyrin and stercoporphyrin (see Garrod, 1923) and possibly others, which, however, are very similar to hematoporphyrin in structure and properties, the term hematoporphyrin has been often used collectively to describe the naturally occurring porphyrins. It is interesting to find in the examination of the literature, that porphyrins are very frequently not demonstrable in the blood or urine of patients showing the lesions definitely associated with the diagnosis of *Hydroa*. This indicates that the porphyrins of this type are not always associated with the condition diagnosed as *Hydroa*, and it also appears doubtful if this particular type of skin lesion always appears as a result of exposure of the skin to the sun's rays. We find actually that some of the *Hydroa* patients in whom the development of the lesions has been quite

definitely associated with exposure to light have shown porphyrins in the blood or urine, while others have not (see Hausmann and Haxthausen, 1929, Barber *et al*, 1926)

Furthermore, an interesting situation appears when we consider the wave lengths active in bringing about skin lesions in Hydroa patients in the few cases in which this has been examined. The results of such examinations are not clearcut but in most cases the sensitivity to light is definitely in the ultraviolet region, with one or two possible exceptions in which there has been some sensitivity to visible radiation (see Hausmann and Haxthausen, 1929, and Barber *et al*, 1926). Now hematoporphyrin and the naturally occurring porphyrins show strong absorption in the visible region around 550 $m\mu$ (see figure 1), and animals sensitized by the injection of hematoporphyrin develop very striking symptoms, including skin lesions, when exposed to light of such wave lengths. The experimental animals in this case include man, as Meyer-Betz (1913) performed the experiment upon himself; it should be noted, however, that although Meyer-Betz developed severe edema of the skin and definite localized skin destruction when exposed to strong irradiation, he did not develop any hydroa-like eruption. He was sensitive to radiations which had passed through window glass which would have been extremely weak in ultraviolet radiation. This experimental evidence has often been invoked to establish the relationship between hematoporphyrin and Hydroa, but the lack of correspondence between the radiations active in the two cases ren-

ders this evidence almost valueless. The naturally occurring porphyrins, uroporphyrin and stercoporphylin, are very similar to hematoporphyrin in chemical structure and show practically the same absorption spectrum. Hausmann and Krumpel (1927) have shown that all these porphyrins show absorption in the violet and ultraviolet with a maximum at about 400 $m\mu$ (see figure 1), and moreover, Hausmann and Sonne (1927) and Lassen (1927) have demonstrated that photodynamic sensitization occurs in this region. Thus it is possible that hematoporphyrin may sensitize Hydroa patients in this region, but no explanation is offered by this assumption for the failure of these substances to sensitize the Hydroa patients to light of 550 $m\mu$.

Fischer has suggested that the porphyrins themselves may not be the photosensitizers, but the porphyrinogens or leucobases of the porphyrins. The porphyrinogens absorb principally in the ultraviolet and thus their sensitizing action would be in this region, the absorption of these substances in the ultraviolet has been demonstrated by Hausmann and Krumpel (1929). Unfortunately, these wave lengths are in the same general region to which the normal skin mechanisms react, so that we cannot easily prove or refute this hypothesis by studying the wave lengths which produce Hydroa. The porphyrinogens are supposedly changed to porphyrins by the action of light, according to this hypothesis, so that we are still presented with the question as to why the porphyrins found in the blood stream do not produce sensitization in the visible region.

Another argument against the con-

cept that this disease is produced by a photoactive substance circulating in the blood is that in certain of the cases studied it was found that only those skin areas which had previously shown the Hydroa lesions could be sensitized by ultraviolet radiation. This would indicate that the reaction produced by this means represents a hyperactivity of the normal erythema reaction brought about by the ultraviolet wave lengths and is not due to an abnormal sensitizer circulating in the blood stream, since in the latter case all skin areas should be light sensitive to approximately the same extent. Furthermore, porphyrins are frequently found in the blood stream and in the urine in conditions not associated with light sensitivity. We may cite as examples the condition following veronal or lead poisoning, often referred to as *hematoporphyrina toxica*, and the idiopathic condition *hematoporphyrina acuta* (see Rothman, 1926, and Mason and Farnham 1931). In these conditions considerable quantities of porphyrin may be demonstrable in the blood and urine, but only rarely are these cases light sensitive (see Hausmann and Haxthausen, 1929).

The problem is obviously much more complicated than we are led to expect, and the exact relationship between porphyrins and Hydroa is certainly not clearly understood. It is quite possible that the porphyrins play no part whatsoever in the light sensitivity or, again, that they represent products of skin injury. The relation of abnormal sensitizers to other light sensitive diseases is still more obscure. Further well-controlled observations on light sensitive cases should prove of great

value in settling this question. It would be of considerable value if observations could be made to determine whether or not individuals showing porphyrins in the blood or urine were actually light sensitive, and if so, whether to visible light as well as to ultraviolet. The latter fact should be determinable by exposing the subject to sunlight with a part of the skin exposed directly, and a part protected by window glass which cuts out practically all ultraviolet radiation active in bringing about the normal skin reactions (see figure 1).

Photosensitization by ingested substances which enter the blood stream occurs in domestic animals. At least two well established instances are the conditions of *fagopirismus* and *hypericismus* which develop when animals are fed upon buckwheat or St. Johnswort respectively. No examples of such sensitization by foods are known in man although the possibility exists. Buckwheat poisoning has been described (Smith, 1909) but this was undoubtedly allergy and not photosensitization*.

Various instances of photosensitization as the result of the therapeutic use of photoactive substances in the clinic have occurred. The substances have sometimes been given by mouth, sometimes by intravenous or subcutaneous injection and sometimes applied to the skin. The earliest example is that of Prime (Hausmann, 1923, p

*The well-established opinions of the laity that "buckwheat rash" develops in the spring, and that buckwheat should not be eaten during the summer months are explainable with difficulty unless buckwheat has a photodynamic effect in man as well as in the lower animals. EDITOR

156) who attempted to treat twenty-six epileptic patients with the bromine containing compound *eosin*. His patients developed a dermatitis and showed damage to the nails, particularly the thumbnail, which was most exposed to light Jausion and Marceron (1925) observed sunstroke ("coup de soleil") in nine of twenty soldiers treated with *trypaflavine* for gonorrhea, dermatitis and excessive pigmentation were described by other observers using various *acridine* preparations (Hausmann and Haxthausen, 1929, p 79-80) Numerous instances of sensitization by acridine compounds have been described for workers using this substance, or substances containing it, in technical procedures The writer has recently been informed of a case in which *rose-bengale* had been used in liver function test, in which obstruction was present so that the dye was retained and the patient was photosensitive for a short time

Dermatitis produced by substances applied to the skin have been described as photosensitizations (see Hausmann and Haxthausen, 1929), some of which may fall under this group The toilet water or "Berlock" dermatitis which has been frequently described within the last few years is probably not a photodynamic effect

It is probably safe to predict that more cases of photosensitization will soon be described, as the use of sensitizing substances in light therapy is being taken up to a certain extent The use of photosensitizers (*erythrosin*) in light therapy was tried out in Finsen's Institute shortly after 1900 and subsequently abandoned It was also tried out by Jausionck and Tappener (1905)

in the treatment of superficial carcinoma with no definite results Recently the use of sensitizers as a therapeutic measure has again been taken up Gyorgi and Gottlieb (1923) claimed to have obtained good results in the treatment of rickets, and Macht and Anderson (1928) for the treatment of pernicious anemia using eosin as a sensitizer Others have apparently applied the treatment to any condition which had at any time been treated by ultraviolet light, the sensitizers used include *trypaflavine*, and *methylene blue* as well as the fluorescein dyes such as eosin and erythrosin

I do not wish to deny the results claimed by these workers, but only to point out certain dangers which present themselves from a more or less theoretical viewpoint Sensitizers of the type used are all known to produce damage to living cells by oxidative processes involving molecular oxygen Other photochemical reactions of the sensitizers may be produced in organic or inorganic systems, e g, the sensitization of the photographic plate, but such have never been demonstrated in living tissues (see Blum, 1932) It seems, for instance, highly improbable, though not impossible, that such substances should sensitize the particular process involved in the treatment of rickets, viz, the transformation of ergosterol to vitamin D, and much more probable that the destructive oxidative effects would predominate The former was apparently the thesis assumed by Strauch (1930) who injected hematoporphyrin into two farmer boys having rickets Strauch observed an erythema in these children upon exposure to light and came to the con-

clusion that the treatment might be effective in curing rickets, he does not state, however, whether the patients recovered from rickets or not. I do not wish to deny that photochemotherapy may have some application, but such methods should not be applied to patients without more animal experimentation, where possible, to establish the results.

The assumption that visible light and a sensitizer will accomplish the same reactions as ultraviolet light is without theoretical or experimental support at the present time. Both accomplish the same gross effect, erythema. The histological effects on the skin are described as being the same

by Levy (1929), but Videbech (1931) states that there is much more injury to connective tissue in the case of the photosensitized erythema, this may be a question of the extent of the irradiation, etc.

The dangers arising from the use of photosensitizers in therapeutics cannot be too strongly emphasized. If such methods are applied, they should at least be used with great caution. It should be remembered that Meyer-Betz (1913) remained sensitive to light for several months after a single injection of hematoporphyrin and that lasting damage can be done by the incautious use of such methods.

BIBLIOGRAPHY

- BARBER, H. W., HOWITT, F. D., and KNOTT, F. A. Some observations on light sensitization, *Guy's Hosp Rep*, 1926, **1xxvi**, 314-341.
- BLUM, H. F. Photodynamic action, *Physiol Rev*, 1932, **xi**, 23-55.
- GARROD, A. E. Inborn errors of metabolism, Chap. viii, *Hematorporphyria congenita*, 1923, Froude, and Hodder and Stoughton, London.
- GYORGY, P., and GORTLIEB, K. Verstärkung der Bestrahlungstherapie der Rachitis durch orale Eosinverabreichung, *Klin Wchnschr*, 1923, **ii**, 1302-1303.
- HAUSMANN, W. Grundzüge der Lichtbiologie und Lichtpathologie, *Strahlentherapie*, **vi** Sonderband, 1923, Urban and Schwarzenberg, Berlin.
- HAUSMANN, W., and HAYTHAUSEN. Die Lichterkrankungen der Haut, *Strahlentherapie*, **xi** Sonderband, 1929, Urban and Schwarzenberg, Berlin.
- HAUSMANN, W., and KRUMPEL, O. Über die Absorption der Porphyrine im Ultraviolett, *Biochem Ztschr*, 1927, **clxxxvi**, 203-212.
- HAUSMANN, W., and KRUMPEL, O. Über die Absorption von Farbstoffen und Leukoverbindung als Vorbedingung der photobiologischen Sensibilization im Ultraviolett, *Biochem Ztschr*, 1929, **ccix**, 142-148.
- HAUSMANN, W., and SONNE, C. Über die sensibilisierende Wirkung des Hamatoporphyrins im Ultraviolett, *Strahlentherapie*, 1927, **xxv**, 174-182.
- JAUSION, and MARCERON. Le «coup de lumière» acridinique. Son traitement préventif par la resorcine, *Bull de Soc franç de dermat et syph*, 1925, **xxxi**, 358-362.
- LESIONEK, A., and TAPPEINER, H. Zur Behandlung der Hautcarcinome mit fluoreszierenden Stoffen, *Deutsch Arch f klin Med*, 1905, **lxxvii**, 223-227.
- LASSEN, H. C. A. Über die Lichtsensibilization im Ultraviolett, *Strahlentherapie*, 1928, **xxvii**, 757-768.
- LEVY, A. G. The pathological action of light, *Jr Path and Bact*, 1929, **xxxi**, 387-399.
- MACHT, D. I., and ANDERSON, W. T. Clinical and experimental studies on phototherapy in pernicious anemia, *Jr Pharm and Exp Med*, 1928, **xxvii**, 365-389.
- MASON, V. R., and FARNHAM, R. M. Acute hematorporphyria (report of two cases), *Arch Int Med*, 1931, **xli**, 467-483.

- MEYER-BETZ, FRIEDRICH Untersuchungen
über die biologische (photodynamische)
Wirkung des Hämatoporphyrins und an-
derer Derivate des Blut- und Gallen-
farbstoffs Deutsch Arch f klin Med,
1913, cxii, 476-503
- ROTHMAN, P E Hematoporphyrinuria, Am
Jr Dis Child, 1926, xxvii, 219-225
- SMITH, H L Buckwheat poisoning (with
report of a case in man), Arch Int
Med, 1909, iii, 350-359
- STRAUCH, C B Photosensitization, Am Jr
Dis Child, 1930, xl, 800-803
- VIDEBECH, H Klinisches, und Experimen-
telles über die Lichtsensibilisation durch
Trypaflavin Mit besonderem Hinblick
auf die lokale Lupusbehandlung, Strah-
lentherapie, 1931, xli, 417-434

The Contributions of Medicine

"IT HAS been inevitable that medical services should be influenced by the various economic and social changes which have developed in this country in recent years. While changes in industrial and community life are having an influence on the health of the people, the enormous growth of knowledge of disease and methods of control and prevention have revolutionized conditions of living during the last fifty years. The death rate at present is only about three-fifths of what it was a half century ago. The virtual elimination of smallpox, typhoid fever, yellow fever, typhus, bubonic plague, and cholera from large areas of the world, the rapid reduction in the incidence of tuberculosis and diphtheria, and the control of hookworm, malaria, and other parasitic diseases suggest a few of the striking contributions which science is making to the safety and comfort of modern life, contributions which in some instances have transformed living and working conditions in large sections of the country. Special attention to nutrition and the influence of foods, minerals, and vitamins on the health of the individual, and efforts to secure a better understanding of the mental processes which is fundamental for a sound program of dealing with human behavior, are likely to result in further contributions.

"No difficulty is experienced in demonstrating that physical and mental health is the greatest asset of a nation as well as of an individual. It is one of the necessities of everyday life. The prosperity and happiness of a people are largely dependent upon mental and physical vigor. Ill health and its effects are recognized widely as one of the major causes of dependency and unemployment. The most pressing health problem is to devise a permanent and comprehensive program of conserving health and treating illness and disability which will become an essential part of the cooperative endeavor known as civilization."

(From the *Final Report of the Commission on Medical Education*, 1932;
WHITARD C RAPPAPORT, A M , M D , F A C P , Director of Study. Pages 17-18)

The Cardiac Complications of Trichterbrust

By JAMES G. CARR, M.D., F.A.C.P., *Chicago, Illinois*

TO an unusual thoracic deformity characterized by an oval or circular, almost funnel-shaped depression of the middle of the anterior thoracic wall, the deepest part of which lies in the sternum itself, the name *Trichterbrust*, the German for funnel-breast, has come into common use in many languages. Von Fruhwald's definition includes a clause making specific mention of the diminution of the capacity of the thorax and Dächter included in his criteria, "Increasing depression of the sternum with the age of the patient and a progressive enlargement of the transverse diameter as the depression is deepened." In one of the earliest contributions to the subject, Eggel had pointed out this last-mentioned feature of the deformity, when he described "a compensation of the spatial defects, produced by the depression of the anterior chest-wall, which is accomplished in three ways (1) the enlargement of the antero-posterior diameter in the mammillary lines, (2) the very significant enlargement of the transverse, and (3) the enlargement of the vertical diameter of the thorax, the latter fact must be concluded from the low position of the upper limit of hepatic dulness and the

displacement of the cardiac apex to a deep position."

It is obvious that such a deformity may cause displacement of various organs and interference with their function. Here our attention will be confined chiefly to the anatomical and physiological effects of *Trichterbrust* upon the heart.

Historically, the credit for presenting the condition to the profession as a clinical entity and for the first use of the name now so generally employed, goes to Wilhelm Ebstein, who in 1882 summarized the reports of five cases in the literature, coordinated them as a single disease-picture and used the word "*Trichterbrust*" to describe the clinical entity. Prior to his publication another case had been reported to which Ebstein did not refer. This was the case of Williams, recorded in the "*Transactions of the Pathological Society of London*" for 1872. The patient in this instance was a "lad of 17" who "was born with this hollow in his chest."

In discussing the history of the subject practically all authors refer to the anonymous communication which appeared in the *Gaz des Hôp* in 1860 as the first description of funnel-breast. In the same year Woillez reported a case with a careful study. It seems likely that Woillez reported

Presented at the San Francisco meeting of the American College of Physicians, April 7, 1932

a patient who had been seen and discussed by Rokitansky in 1857, a medical student from a German University who was making the rounds of the medical schools of Europe about that time (E von Ebstein) W von Ebstein mentioned that the local Pathological Institute at Gottingen contained a plaster cast designated as demonstrating "congenital collapse of the sternum" which completely conforms to the deformity described Prof Orth was authority for the statement that the plaster model dated from 1850. An even more interesting note on the historical aspects of this subject was contributed by Erich von Ebstein in 1921, the author of an extensive article on Trichterbrust in 1909. In this brief reference the statement is made that attention had already been paid to these conditions by the end of the sixteenth century. A short, excellent observation occurs in the principal work of the Freiburg physician, Johann Schenck, of Graefenberg (1531-1598). He set for himself the difficult but very useful task of collecting the literature on a large scale. In order to make this possible he was not satisfied to take from works at hand and to add cases from his own large practice but he was in communication with the foremost correspondents of his time. He quotes Johann Bauhinus who described the principal clinical symptoms—"dyspnea, associated with cough increasing to paroxysms of suffocation". From this same Bauhinus is quoted a description of a case in which "The sternum with the ribs was turned inward from birth, causing difficulty of breathing. The patient was a boy of seven in whom

the ensiform cartilage was turned toward the interior of the body so that a great cavity appeared" Doubtless the funnel-shaped breast described by Eggel in 1871 as "A Rare Deformity of the Thorax" has not actually been so uncommon as early writers presumed.

As to the anatomical characteristics of Trichterbrust, Wolostnich says there is practical agreement as to the following picture "The upper limit of the Trichterbrust is formed by the connecting line between the manubrium and corpus sterni, from this situation the funnel-shaped depression runs downward and backward, in most instances the greatest depth is reached at the scrobiculus cordis. The rounded base has a very slight extension, the diameter of which is variable. From the base of this depression its wall runs forward in such a manner, corresponding to its funnel-shape, that on the anterior wall of the body the maximum breadth varies between 9 and 17.2 cm. The center of the depression is not always in the middle of the sternum and the line of depth of the furrow is not always straight." This circular or oval depression at the lower end of the sternum may reach a depth of several centimeters, as much as 6 or 7. Picqué and Colombani measured the capacity of the depression in cubic centimeters of water. In the less pronounced cases this amounted to about 50 cc but in the more severe to 170 cc or more.

As one result of this depression various degrees of cardiac displacement have been reported. Versé studied the thorax of a female subject who died at the age of 48 years. The

thorax was removed *in toto* and hardened for two days. The lower end of the corpus sterni included the deepest part of the depression and almost touched the spine at the level of the cartilage between the tenth and eleventh thoracic vertebrae. Here the distance from bone to bone measured only about 1 cm. This could be increased to $1\frac{1}{2}$ cm by lifting the sternum. The thin cartilaginous process xiphoides was 4 cm long and directed obliquely forward, its tip was distant from the spine 37 cm. The chief mass of the heart was found to the left of the midline. Almost the entire left ventricle and a small part of the left auricle with the greatest section of the mitral valve were found lateral to the left parasternal line. Von Bien reported an autopsy at which the heart was found to lie "entirely in the left half of the thorax, while the right half was filled by the lungs, behind the heart a thin half-moon-shaped section of the lung was seen. The heart in its entirety was displaced to the left. If one drew the median line of the body in such a way that the line of the ensiform process was connected with the most ventrally situated points of the vertebrae it so happened that not a single section of the heart lay in the right half of the body. But corresponding to the displacement of the sternum to the left a part of the heart was in contact with the inner surface of the sternum, a small portion of the anterior wall of the right ventricle and a small part of the right auricle attached thereto. If, at the place of deepest depression, one lifted the anterior wall from the heart a deep depression of the auricle was seen

which extended to a portion of the right ventricle." In this case the displacement involved the roots of the vessels at the base of the heart. At the time of his report in 1920, Stadtmüller stated that he could find in the literature only eight reports of autopsies, in four of these the subjects were adults. He added the report of an autopsy upon the body of a man of 60 and stated that the heart showed (1) total displacement to the left and (2) the appearance of being turned about its sagittal axis. Von Hoffmeister quotes Henschen and Nageli as having observed a significant pressure point on the right ventricle. Rudolph von Pohl has described another type of cardiac involvement in those cases of Trichterbrust in which the median position of the heart is retained. "The thoracic deformity produces an indentation of the heart in front, corresponding to the in-bowing of the anterior thoracic wall, and the anteroposterior cardiac diameter is diminished."

Clinically, displacement has frequently been noted. In recent years roentgenological examination has confirmed this finding. Sauerbruch stated that "by physical examination and the roentgen-ray one may determine displacement of the heart to the left with or without simultaneous rotation about its axis." L. Meyer, von Hoffmeister and Alexander all wrote of the demonstration of displacement to the left by means of the roentgenological examination. Von Rosler, discussing the results of examination by the X-ray in cases of thoracic deformity, remarked regarding Trichterbrust "It is plausible that in high-grade cases,

through the flattening of the heart the cardiac work is unfavorably influenced, the normal systolic-diastolic change of form and rotation must be made difficult, the circulatory relations of the blood in the heart itself, probably also the position and form of the venous openings, may be changed."

In spite of the marked deformity, the changes in the dimensions of the space normally occupied by the heart and the anatomical evidence of change in the position and even of the shape of the heart, those who have contributed to our knowledge of the subject are not agreed as to the effect of the deformity upon cardiac function. Von Eggel's patient, in whom the distance from the deepest part of the sternum to the corresponding vertebral spine was only 11 cm (according to Vierordt the normal distance from the ensiform to the thoracic spine is 15 to 19 cm), "could not lift such heavy burdens nor run as fast as others of like occupation, but without distress he carried on his work as an efficient farmer, walked with firm tread and showed no trace of dyspnea, to say nothing of cyanosis. When he was six years old his physician had predicted that he would not outlive his twentieth year. Within four weeks of his birth the breast was so sunken that an egg could have been laid in the furrow." In von Flesch's case, although the depression was extreme, "respiratory pains had never been present, even hard work can be done without dyspnea." Graeffner made a similar observation. In 1911, Groedel reviewed his records for cases of Trichterbrust and reported three well-marked instances. It was his opinion that satisfactory

evidence was not at hand to warrant the assertion that this deformity is responsible for cardiac failure. He contends that while Trichterbrust does change the form and shape of the thorax, it does not change the content. The lung accommodates itself to displacement as does the heart, without necessarily involving these organs in functional damage. Groedel raised a question of interest and importance in the determination of the relationship of symptoms to the deformity. He emphasized the frequent association of Trichterbrust with the habitus asthenicus, in which condition are often found symptoms of circulatory embarrassment similar to those described as resulting from the displacement or pressure produced by Trichterbrust. In the latter condition surgical procedures to relieve dyspnea or other disturbances attributable to impairment of cardiac function must be based upon a conviction of the relationship between the deformity and the symptoms. The frequency of associated stigmata of the habitus asthenicus calls for careful consideration as to the amount of permanent relief which may be expected by surgical treatment of the deformity. In this connection we may quote again from Wolostnich who reviewed the literature thirty years after the first publication of von Ebstein. "The function of the heart and the pulmonary capacity commonly remain normal. The affected individuals have no pains from their Trichterbrust and very often—as is definitely stated in many works—the whole deformity presents an accidental and incidental finding upon the examination of a patient who has sought the

physician for other reasons" Kuhns has recently expressed this conservative statement "With careful pathological studies and fuller understanding of the physiological disturbances which such displacement of thoracic and abdominal viscera produces, has come an appreciation of the rôle of this condition in inducing fatigue, subnormal health and disease"

While in general these views of the lack of demonstrable connection between the deformity and cardiac or respiratory symptoms have been dominant since the condition was first described, attempts have been made, first by orthopedic procedures and later by surgery, to correct the deformity and thereby relieve associated symptoms attributed by the operators to the deformity In 1911, Ludwig Meyer performed the first operation for such relief He prefaces the description of the technic with a discussion of the case and remarks that "The literature tells us little or nothing of the symptoms which result from the deformity

For a patient of this sort, when he suffers from dyspnea, therapy can only be effective when it changes the anatomical conditions fundamentally and provides conditions compatible with respiration" The operation consisted in the removal of the second and third costal cartilages of the right side, each about $2\frac{1}{2}$ cm in length Von Hoffmeister, reporting a case from Lexer's clinic in 1927, implied that the result in Meyer's case was not satisfactory After describing resection of a considerable portion of the sternum in a young man whose symptoms were dyspnea upon exertion, sticking pain in the region of the heart and palpi-

tion, he makes this remark "That only an extensive removal of the diseased portion gives a result, the unsuccessful attempt of L Meyer has shown" Sauerbruch reported a successful operation upon a young man of 18 years with congenital Trichterbrust, whose symptoms were cardiac irregularity and dyspnea upon exertion The operation was undertaken because "the patient was not able to do his work in his father's watch factory, since the least effort caused palpitation and a feeling of oppression" After some two or three weeks in the hospital, prior to operation, a short walk on a street with a moderate rise produced "marked cardiac irregularity and dyspnea" which were attributed to a mechanical interference with cardiac function It was the surgeon's idea that "removal of the rigid funnel would give more room to the heart and free it from the constricting pressure of the thoracic wall" On the left side the costal cartilages with portions of the sixth to the ninth ribs (the length of each resected portion was about 3 cm) and about one-half of the sternum corresponding, were removed The post-operative course was smooth Three years later the patient had gained weight, felt well and was working twelve to fourteen hours a day Von Hoffmeister reported from Lexer's clinic the case of a young man of 19, who had complained for two years of cardiac pain, dyspnea upon exertion and palpitation Below the attachment of the fifth rib the sternum with the costal cartilages was removed Twelve weeks after operation the general condition was essentially improved, there was a gain in weight and dyspnea

was present in only slight degree. The pains in the heart were definitely less in comparison to those earlier observed. Zahradnicek reported the case of a boy of 16 with a high degree of funnel-shaped chest. The sagittal diameter at the point of depression was about 10 cm. The patient was dyspneic and had palpitation. The operation consisted in perforation of the sternum and the introduction of two wires which were used for traction. The result was quite satisfactory. Two cases of "traumatic pectus excavatum" were reported by Alexander in 1931. A boy of 16, whose depression had followed an injury while wrestling, complained of dyspnea and occasional dysphagia.

Ten months after operation the patient wrote that he had no pain nor dyspnea even upon exertion, and that the correction of the deformity was maintained. The second patient was a woman of 20 whose deformity followed an automobile accident. She complained of severe pain in the region of the heart, of dyspnea and palpitation. The pain was usually referred to the left shoulder. The cardiac pain was disabling and unrelieved by long rest. She had no cardiac, shoulder or left axillary pain after the operation.

These few cases serve to confirm Sauerbruch's opinion that "high-grade disturbance of cardiac and pulmonary function with signs of congestion in the peripheral vessels may occur." Proper selection of cases justifies surgical interference in certain cases of Trichterbrust. Two important principles should govern the decision as to operation in any given case. (1) Trichterbrust is not in itself an indi-

cation for operation, (2) there should be a high probability of relationship between the symptoms and the deformity before operation is justifiable. An interesting sidelight on the conditions proposed is derived from Gerstenberg's monograph published in 1904. He compiled a list of twenty-one published cases in which the measurements of the deformity had been given. The oldest patient in this group was 39 years of age. One may conclude that the condition is sufficiently disabling to bring its victims to the attention of the physician in early life. This fact alone should stimulate us to continued effort in our search for a means of relieving the deformity which forebodes only increasing disability and shortening of life. To experienced and careful surgeons, especially to those skillful in thoracic work, the indications for surgery just mentioned may reasonably be liberalized in the presence of individual problems.

CASE REPORTS

In the past year two cases of Trichterbrust with cardiac symptoms have come under our observation. The *first* patient was a young woman of 19, unmarried. She complained of rapidity of the cardiac action and a feeling of faintness and dyspnea upon exertion. She had never been strong. She had had measles, chickenpox, pertussis and pneumonia in childhood. During her twelfth year she had several attacks of fainting and was unable to attend school. During the last two years she has had fainting spells which were responsible for several falls, in one of which her left arm was broken. Three times within two years she has attempted to take training for the nursing profession, only to be sent home after a few weeks, because of her health. From the last hospital training school which she attended she was

discharged with a diagnosis of mitral disease. She has consulted many physicians. Several specimens of sputum have been examined without the discovery of tubercle bacilli. Once a diagnosis of pulmonary tuberculosis was made roentgenologically. Epilepsy has been diagnosed. Tonsillectomy has been done. Strychnine has been taken over long periods of time, under this therapy she became sick and restless.

The patient was a thin sickly young woman with moderate cyanosis of the lips. There was no evidence of disease of the lungs. The left border of the heart was $7\frac{1}{2}$ cm to the left of the midsternal line, the right $1\frac{1}{2}$ cm to the right. A systolic murmur was heard over the precordium, most distinctly at the base and over the left side of the back to the inside of the scapula and

below it. Except that the lower pole of the right kidney was palpable the abdomen was negative. Normal reflexes were present and pathological reflexes were not elicited. The cardiac rhythm was regular, the rate 112 (after entering the hospital the rate varied between 90 and 100), the blood pressure was 130/90. The blood count was essentially normal. The urine was negative. The basal metabolic rate was -4.6 per cent. The electrocardiogram showed normal mechanism with a diphasic T in Lead 2, a negative T in Lead 3, slurring near the apex of the R-spike in Lead 2 and deep splitting of R in Lead 3. Roentgenological examination of the chest showed a heart of normal size slightly displaced to the left, the right border showed indistinctly, which was attributed by the roentgenologist to pleuro-



FIG 1 Lateral roentgenogram of the chest of the first patient, who was operated upon

pericardial adhesions, although fluoroscopically free movement of the heart was demonstrated. The lateral plate showed marked depression of the sternum. The distance from the eleventh dorsal spine to the point of maximum depression of the Trichterbrust measured 13 cm.

the lower end and behind the xyphoid." Following the operation the cardiac rate fell to 70 to 80 and remained so for a day, then slowly went up over two or three days to 120 and receded within a few days to 80 to 90.

Four weeks after her discharge the pa-



FIG. 2 Photograph of the second patient

After ten days of observation this patient was operated upon by Dr. Jerome Head. "On the left side the 3rd, 4th, 5th, 6th and 7th costal cartilages were removed and on the right side the 4th, 5th, 6th and 7th. The lower one-half of the sternum together with the xyphoid was resected. The pectoral muscles were drawn together in the midline over the upper half of the defect. The fascia and subcutaneous tissues were closed similarly over the lower part of the defect. At the beginning of the operation the pulse rate was 100, coincident with the removal of the cartilages on the left the pulse dropped to 65. When a finger was inserted beneath the sternum the heart pressed against the finger, especially at

the lower end and behind the xyphoid." Following the operation she had lost her cardiac consciousness and was walking a mile or more daily. After another three months continued improvement was reported. At this time the murmur noted prior to operation was confined to a small area about the second and third interspaces to the left of the sternum. Nine months after the operation she was seen again. At this time she was not doing so well. The original cardiac symptoms were not present but the patient was nervous and had lost some weight, (following the operation she had gained). An unhappy domestic situation was probably responsible for the nervous symptoms then present.

The second case was that of a boy of 13

years, who was referred to us from the Children's Memorial Hospital, where he had been under treatment for hemorrhage from a duodenal ulcer. The patient when first seen was cyanotic and moderately short of breath. He weighed 78½ pounds. The temperature was 97.8, pulse, 84, respirations, 20. The blood count was normal. The distance from the second thoracic vertebra to

yet sure enough of our ground to urge surgical interference without such symptoms as may be regarded as making an operation mandatory if the patient is to live without actual distress.

SUMMARY

1 Trichterbrust is the term applied to a characteristic deformity of

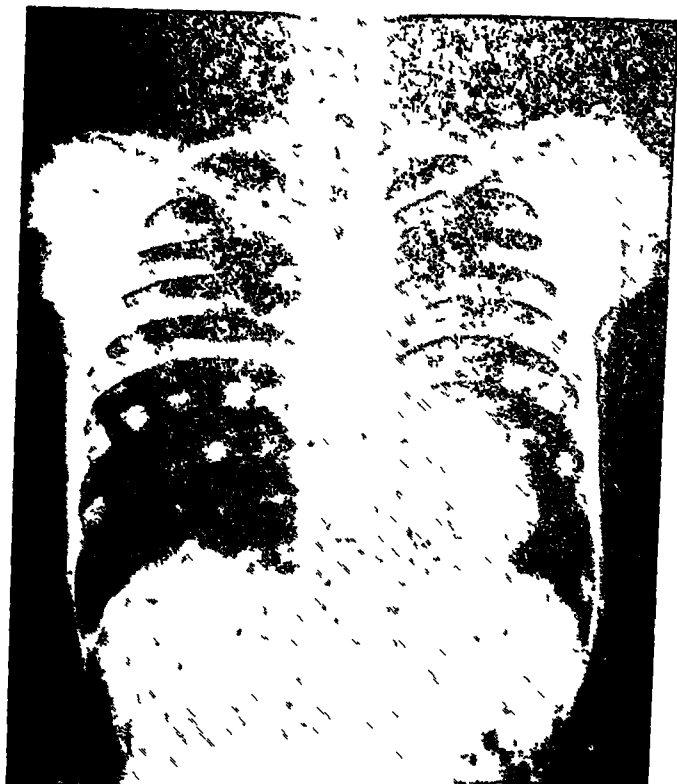


FIG 3 Antero-posterior roentgenogram of the chest of the second patient

the sternum was 10 cm, the anteroposterior diameter at the point of deepest depression was 8 cm. The width of the depression was 11 cm, the depth, 4 cm, and the vertical diameter, 14 cm. The apex was in the fifth interspace, 10½ cm to the left of the mid-sternal line, the apex rate was 84, the blood pressure, 104/82. The X-ray plate showed displacement of the heart to the left and a widening of the transverse diameter. Three months after the first examination the cyanosis was rather less marked, the dyspnea definitely less. Operation has been discussed with the father but not urged, we are not

the sternum, with depression thereof, resulting in pressure upon the heart, usually with displacement. Definite cardiac symptoms are not the rule in these cases, but such do occur. Dyspnea and palpitation are the most common symptoms.

2 Operative procedures have been reported, especially in recent years, with good results. Another case is here reported in which operation was followed by prompt amelioration of

the symptoms. A smooth post-operative course, such as this patient presented, is not always to be expected. Since the operation reported, Dr Head has operated upon another patient, not mine to report, who died within forty-eight hours following the operation.

3 In anticipation of operation, care should be taken to differentiate the cardiac effects of the deformity from the cardiac symptoms of the habitus asthenicus. Only in case the symptoms may reasonably be attributed to the former is surgical treatment justifiable.

BIBLIOGRAPHY

- VON FRUHWALD, H. E. Zwei Fälle von kongenitaler Trichterbrust, Beitr z path Anat u z allg Path, 1913, lvi, 13-21.
- DRACHTER. Thorax, Respirationstraktus und Wirbelsäule, 1907, Sauerbruch, 1c.
- VON EGGEL. Eine seltene Missbildung des Thorax, Virchows Arch f path Anat, 1870, xlix, 230.
- VON EBSTEIN, W. Über die Trichterbrust, Deutsch Arch f klin Med, 1882, xxx, 411-428.
- WILLIAMS, C. T. Congenital malformation of the thorax, great depression of the sternum, Tr Path Soc, London, 1872, xxii, 50-52.
- ANONYMOUS. Difformite thoracique, Gaz d hop, 1860, xxxiii, No 3, 10.
- WOLFF. Sur un cas de difformité thoracique considerable, avec déplacement inoffensif de plusieurs organes et signes stéthoscopiques particuliers, Union méd, 1860, vi, 2 Série, 515-521.
- VON EBSTEIN, E. Über die angeborene und erworbene Trichterbrust, Samml klin Vortr, (Inn Med), 1909-1910, cxvii-cxviii.
- Zur Geschichte der familiären Trichterbrust, Deutsch med Wchnschr 1921, xlvii, 1070-1071.
- WOLOSTNICH, N. Über Trichterbrust, Inaug. Diss., 1913, L. Fiebering, Berlin.
- PIQUET, L., and COLOMBANI, J. Etude sur le thorax en entonnoir (type Ebstein), Rev d'orthop 1900, 1 2 Série, 157-196.
- Voss, M. Über die kongenitale Trichterbrust mit besonderer Berücksichtigung der normal-anatomischen Verhältnisse, Beitr z path Anat u z allg Path, 1910, xliii, 311-342.
- PIQUET, L. Zur Anatomie und Ätiologie der Trichterbrust, Beitr z path Anat u z allg Path, 1912, xliii, 567-576.
- VON STADTMÜLLER, F. Kurze Mitteilung über die anatomische Untersuchung eines Falles von Trichterbrust, Beitr z path Anat u z allg Path, 1920, lxxii, 528-532.
- HENSCHEN AND NAGEL. Handb d prakt Chir, 1924, F. Enke, Stuttgart, vi, 563. Sauerbruch, 1c.
- VON POHL, R. Trichterbrust und Herzform, Wein klin Wchnschr, 1928, xli, 1439.
- MEYER, L. Zur chirurgischen Behandlung der angeborenen Trichterbrust, Berl klin Wchnschr, 1911, xlviii, 1563-1566.
- VON HOLZMEISTER, W. Operation der angeborenen Trichterbrust, Beitr z klin Chir, 1927, cxli, 215-223.
- ALEXANDER, J. Traumatic pectus excavatum, Ann Surg, 1931, xciii, 489-500.
- VON ROSIER, H. Zur röntgenologischen Beurteilung des Herzgefäßbildes bei Thoraxdeformitäten, ((Kypho) — Skoliose, reine Kyphose, Trichterbrust), Deutsch Arch f klin Med, 1929, cxiv, 365-377.
- VIERORDT, K. H. Anatomische, physiologische und physikalische, Daten und Tabellen, Zum Gebrauche für Mediziner, 3 Aufl, 1906, G. Fischer, Jena.
- VON FISCHER, M. Über eine seltene Missbildung des Thorax, Virchows Arch f path Anat, 1873, lvii, 289-294.
- GRODDEL, F. M. Das Verhalten des Herzens bei kongenitaler Trichterbrust, Münch med Wchnschr 1911, lvi, 684-686.
- SAUERBRUCH, E. F. Die Chirurgie der Brustorgane 1920, J. Springer, Berlin vi, 437-444.
- GEISTENBERG, C. C. W. Über Trichterbrust 1911, Inaug. Diss. Göttingen.

An Unusual Speech Disorder following Encephalitis Lethargica: Its Interpretation and Therapeutic Management

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IN reviewing the various sequelae of encephalitis lethargica reported by observers one is surprised at the multiplicity of phenomena in the different spheres of human organization. The sensory system in general, the special sensorium, the motor-system at its various levels, the vegetative sphere, the sympathetic nervous system, finally the psychic functions in general, including the affective status, may all isolatedly or conjointly become involved. Data are continuously accumulating. Many varieties of tic-like movements and analogous hyperkinetic manifestations have been observed and described. Some of them are relatively frequent, such as oculogyric crises, other manifestations are more or less rare, such as speech disturbances. Since 1922 there have appeared occasionally in the literature cases in which the tongue would be involved, namely propulsion followed by retreat, frequently or continuously repeated.¹ Smacking of the lips or continuously moistening the lips,² contraction of the muscles of the tongue between

the teeth,³ and vibratory or myoclonic contractions of the tongue have also been reported. In W. Sterling's case,⁴ there was a linguo-salivary symptom perpetually vibrating tremor alternating at times with paroxysmal trepidation of the myoclonic type so violent that saliva would run out of the mouth. The manifestations presented by the two patients described below are exceptional, and perhaps have not been observed before. They concern the buccal cavity, lips, chin, and especially the tongue which renders the speech unusual. This condition presents an additional postencephalitic phenomenon among the large number already observed. The cases here described are excellent examples for a somewhat different interpretation of affective manifestations in a condition which, generally speaking, has an organic basis, with the result of favorable therapeutic management.

CASE REPORTS

Case I S. S., female, age 17. Four years ago, following a slight febrile condition, she began to observe a mild impediment of speech. This condition progressed and became more and more pronounced for a time, but for the last two years the condition has been stationary.

Her present condition is as follows. In

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speaking her tongue has a tendency to protrude between the teeth. In the beginning of her speech, the tongue rolls, curls, and places itself mostly on the right side. The muscles near the angles of the mouth and those of the chin contract more than the other muscles of the cheeks so that two deep furrows appear on both sides of her mouth. It seems that all the other muscles of her face remain immobile while the lip muscles function. This is observed in the beginning of her attempts to speak. The speech itself becomes indistinct, the tongue is always in the way. It may give the impression of stammering, but it is not. There is no evidence of aphasia, or paraphasia, of anarthria or dysarthria.

There is also noticeable, while speaking, a peculiar state of the lower jaw, namely a tendency to droop so that she frequently puts her hand under her chin to hold it up. While there is no paralysis of the tongue, as it can move in all directions, nevertheless the food remains in the mouth a long while and at times there is some difficulty in swallowing. The patient also complains of pronounced salivation. Examination of the buccal cavity fails to reveal any motor or sensory involvement of the muscles of palate and pharynx.

About six months ago the patient says she began to observe a gradually oncoming weakness of the right upper extremity. Examination reveals a certain amount of weakness of every segment of that limb and a fine tremor of the hand. She claims to have difficulty in threading a needle or doing other fine work.

Further examination shows increased knee-jerks but no other pathological reflex. In respect to serology, blood, eyes, sphincters, and sensations there are no abnormalities.

Case II J. B., female, age 19, had five years ago an attack of a depressive psychosis from which she made a complete recovery. Two years ago following a slight febrile state, she developed a speech disorder from which she is suffering now. One year later she developed a tic of the face.

The mode of development, pro-

gressive course and the present state of the speech difficulty, are all identical with those of the first case, except that they are more pronounced. The position of the tongue, the condition of the muscles of the angle of the mouth and of those of the chin are also the same as in the first case. In addition to this, the patient also complains of food and liquids running out of her mouth during mastication.

It is interesting to note that this patient like the first one also presents a weakness of the right upper extremity in every segment of it. Her grip of the right hand is 50 and in the left 60 on the dynamometer, although like the first patient she is right handed. A detailed examination shows that in every other respect this patient is normal somatically.

If the two cases are postencephalitic it is to be presumed that the speech disorder like all the other sequelae reported in the literature is due to a lesion in the striatum with the usual structural damage. A question arises as to the possibility or impossibility of explaining the distorted speech on this purely organic basis. It is indeed difficult to admit that a direct injury to the striate body would be the sole cause of so many somatic, vegetative, and psychical manifestations as constitute the various groups of postencephalitic manifestations. A close examination of the mode of speaking of these patients leads to the conception of a purposeful pattern which originated four and two years ago respectively and remained as such up to the present. Both patients had difficulties of an affective character at the onset of the disorder and as an outlet from the states of anxiety in which they found themselves they developed a substitution or a compensation phenomenon in the form of a compulsion neurosis.

DISCUSSION

An analysis of the identical peculiarity of speech in both patients does not permit one to classify it as a manifestation of aphasia or paraphasia, anarthria or dysarthria. The typical symptoms of the latter are not existing. Besides, the mode of onset, the lack of an acute insult to the parts of the central pathways of speech, the absence of phenomena which usually accompany organic speech disorders,—all these data are absent in the histories of our patients. A close examination of all the peripheral elements which enter into the formation of syllables and words in speech shows that the disorder lies in the improper and abnormal use of the many small muscles which are at work in the enunciation of words. The irregular display of the muscles of the tongue, lips, of the angles of the mouth, and of the chin described above, are sufficiently striking to exclude the possibility of organic dysarthria or aphasia.

Hypertonia or dystonia and hyperkinesia are very frequently met with in encephalitis lethargica and are quite characteristic of postencephalitic parkinsonism, these muscular phenomena may be generalized or limited to circumscribed areas. In our cases there was a history strongly suggestive of a brief attack of encephalitis and as a sequela there remains an irregular muscular function confined to the peripheral agencies used in the formation of letters, syllables, and words.

When an attempt is made to find an explanation of this speech disorder, one naturally turns first of all to the pathological substratum commonly found in the parkinsonian syndrome. Although

lesions have been found at many levels of the brain, cerebellum, medulla and even spinal cord, nevertheless the striatal region occupies the center of attention. In fact almost all the varieties of postencephalitic phenomena have been explained on the basis of damage to the striatum. If motor or sensory disorders, hypertonic or dyskinetic disturbances may be due to an interruption in the structural connection of the striatum with various important segments of the central nervous system, thus explaining directly the anatomophysiological morbid manifestations, it leaves us in total ignorance with regard to the complex psychical phenomena which are so frequently observed in postencephalitic states. Alterations of character, disposition, behavior, radical changes in the affective state have been so frequently recorded¹. Are we in a position to speak of the striatum as a center for affective-psychic functions? Even if we could indulge in such a speculation, would this cover the ground? Could it explain why the postencephalitic individual blinks his eyes, and turns his eyes only in a certain definite direction in cases of oculogyric crises? Can it explain why in our two patients the speech is particularly disturbed when they meet strangers or when they are called upon to answer questions or when they have to participate in games, plays, etc.? The second patient relates that the speech disorder developed first, blinking of the eyes followed when the former began to improve. Presently both phenomena appear simultaneously, one reinforces the other when the patient attempts voluntarily to improve one of them. To content oneself with the

statement that the striatal system alone is the causal factor in all the varieties of affective or psychical abnormalities following an attack of encephalitis, would not be scientific

In our two cases the speech disturbance and in one of them also the association of the eye blinking with the speech are closely connected with certain affective situations in the past as well as in the present

Patient S S was obliged to leave the regular school unfinished to prepare herself for a salaried job in order to help out her relatives. She was in a state of great anxiety about the uncertainty of her heroic efforts. She deprived herself of necessities in order to accomplish her purpose. She is still working in this direction. In the midst of such an anxiety state and evidently because of it, she developed a tendency to walk, act and talk rapidly. She would become irritated, would make extreme efforts to refrain from giving sharp answers, from insulting the people who helped her financially during her preparation period. In addition to this there is another anxiety element in the life of this patient. Because of her home situation she is unable to participate in the pleasures of life: she is obliged to deny herself attending parties, dances, excursions to which she has been frequently invited. When occasionally she visits her friends and finds herself in a crowd she is seized with fear of not being able to keep up with the rest. Her speech becomes then particularly indistinct.

In patient J B, there is also a history of a state of anxiety but of a different origin. About the time of her first attack of encephalitis, she led a

life of extreme comfort, without even being forced to apply herself in acquiring knowledge. At the early age of 15 she received considerable attention on the part of her friends. One of her boy friends became unusually friendly and began to court her. She showed great fondness for him. At the time of her encephalitis her parents forbade him to call. The boy never returned. Having found out the cause of his abrupt abandonment of her, she had a number of violent altercations with her father. She became depressed, isolated herself, and could not sleep. In order to help her out the parents gradually induced her former friends to resume their friendship and to show her the same attention as before her illness. She then noticed a gradually oncoming difficulty of speech. At first it would occur only in the presence of male friends but later also in the presence of females. When therapeutic attempts were made to improve her speech, the blinking of the eyes would appear. Gradually both conditions became fixed and presently both phenomena are simultaneous. She is greatly depressed, refuses to appear in public and the unintelligent comments of her parents on this disorder contribute to its deeper fixation.

We observe a state of anxiety in both patients. In the first case, the fear of being unable to accomplish what she set out to do, also the long isolation and the shut-in existence which made her exceedingly shy and fearful of not being able to entertain and converse with people who made friendly advances to her finally led to the development of a compulsion neurosis in the form of a distorted speech.

In the second patient, the sudden abandonment of a male friend rendered her much depressed. She remained in this state a long time, refused new associations and finally when an effort was made by the parents to correct the situation, the patient began to hesitate in addressing others and thus developed the compulsion neurosis in the form of a distorted speech and later on of blinking as if she felt embarrassed in the presence of people and could not look straight in their eyes.

Both phenomena, the distorted speech and the blinking movements, are of the same order, they are defence reactions against an unconscious command. It is therefore evident that the compulsive phenomenon in both cases is a purposeful pattern and it originated from sources of an affective nature. The serious subjective state of both patients is their great anxiety which stands out as a conspicuous exteriorization of their inner life in the form of psychomotor phenomena of a compulsive character. The purpose behind the tongue or eye movements is self-evident. The latter merely represent a physical maladaptation phenomenon or a compulsive behavior reaction in the lives of two organisms. To understand fully an organism in its activities it is absolutely necessary to view it not merely as a structure but also, and especially, to see its background at all levels of its adaptive ability. A functional purposive level will always be revealed. If such a conception of compulsive situations is admitted by the therapist, some favorable results may be expected from a judicial application of the principles discussed above. In the two cases described

above the fact of an organic insult to the midbrain and particularly to the striatum could not be altogether denied. It was also evident that the exclusive acceptance of an organic structural substratum disarms one from any attempt to remedy the morbid situation. On the other hand, granting the existence of a pathological lesion, if an effort is made also to consider the inner life of these patients and what lies at the main nucleus of their anxiety state, thereby directing attention more to the positive side of the situation, therapeutic results may be expected. Such a procedure brought fruit in our two patients, when we succeeded in demonstrating to them the logical connection of their anxiety with the affective experiences in their life. Progressive improvement is noticeable in spite of the possible existence of an organic lesion.

SUMMARY

An unusual postencephalitic sequela is described as observed in two patients. Attention is called to the fact that in addition to an organic lesion ordinarily found in encephalitis there are other factors of a functional character which may elucidate the nature of the multiple postencephalitic disorders observed so frequently. An organic lesion *per se* will not explain its *modus operandi* in creating all these disorders, especially those of an affective character. Recognition of this principle is of high value in therapeutic endeavors. The two cases described present an excellent illustration of this contention. The occurrence of the speech disorder described adds another though rare phenomenon to the large number of postencephalitic sequelae already known.

REFERENCES

- ¹DUBOIS, C. Un curieux tic de la langue d'origine vraisemblablement postencéphalitique, *Rev. Neurol*, 1929, 1, 40-45
- ²BING, R. Zur Frage des "Parkinsonismus" als Folgezustand der Encephalitis lethargica, *Schweiz med Wchnschr*, 1921, 11, 4-12
- BING, R. Über lokale Muskelspasmen und Tics, nebst Bemerkungen zur Revision des Begriffes der "psychogenie", *Schweiz med Wchnschr*, 1925, vi, 293-1000
- ³CHRISTIN, E. Note sur un cas de contracture de la langue postencéphalitique, *Rev Neurol*, 1922, xxix, 1184
- ⁴STERLING, W. Pahlalie et le symptôme "linguo-salivaire" dans le parkinsonisme encéphalitique, *Rev Neurol*, 1924, xxxi, 205-220

Introduction to Clinical Medicine

"HISTORY taking, one of the most important disciplines of medical training, should familiarize the student with the life history and distinctive features of the onset, symptoms, and course of at least the common diseases and those with which they are most likely to be confused. It is very important that this early period of preliminary clinical training should be under the direction and supervision of the older and experienced members of the faculty, in order to secure the most satisfactory results and to establish a sound basis for the subsequent work of the student. With an experience in history taking, physical examination, laboratory diagnosis, and the use of instruments of examination, the student should be prepared to begin the study of clinical medicine.

"Teachers of clinical medicine should make it clear to students that many of the special examinations made in teaching hospitals are to show the student how knowledge is acquired and to supply complete data on a given patient for the purposes of instruction, not as an illustration of the actual requirements of practice. The specialized examinations and instruments can only supplement, they cannot supplant or substitute for, the direct clinical study of patients. Probably the overemphasis on special examinations by recent graduates and the tendency for them to seek practice in a specialty is partly due to the wrong emphasis in their clinical teaching.

"Students should be made to realize from the beginning of their clinical studies that the diagnosis in a large majority of illnesses can be made on the basis of a searching history, a thorough physical examination, relatively simple laboratory determinations, and the thoughtful consideration of the problem presented. The needs of a majority of patients can be solved by well recognized, relatively simple clinical methods. Some patients present functional disturbances which require considerable patience, time, sympathy, and an insight into the factors responsible. Only a small proportion need the services of specialists for a diagnosis. The physician and the student should be aware, however, of the importance of these special examinations as supplementary aids to established methods of clinical study in certain instances. An important feature of practice is the discrimination and judgment the physician should use in the selection of the time and type of such supplementary aids."

(From the *Final Report of the Commission on Medical Education*, 1932, WILLIAM C. RUTLAND, A.M., M.D., F.A.C.P., Director of Study. Pages 197-198.)

Oral Administration of Metaphen in the Treatment of Gastric and Duodenal Ulcers

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THE opinion is at present generally held that many patients with ulcer belong to the spasmophilic-vasoneurotic type, and therefore antispasmodic drugs, such as atropine and belladonna, in conjunction with the Sippy diet, are used in the treatment of ulcers and nervous dyspepsia. However, it is the opinion of the author (and also that of many other neurologists) that more attention must be paid to direct treatment of the stomach and the intestines, and that one should not rely exclusively on the above and on general methods of psychotherapy and physiotherapy, as, for instance, drug sedatives and stimulants. In the direct treatment of ulcers, the drugs commonly used are sodium bicarbonate in large quantities, chalk of magnesia, bismuth preparations and silver nitrate. Tincture of iodine in five drop doses in a wine glass of water has also been recommended.¹

Early in 1928, the author began administering to psychoneurotic patients who present symptoms of chronic abdominal distress, 3 cc of the 1:500 solution of metaphen, with most gratifying results. In fact, the author feels that a more rapid cure of the psychoneurotic state has been thus obtained

in almost every case, than he has been able to accomplish by any other method. His opinion is based entirely on personal experience, as no literature concerning the use of metaphen in the treatment of gastro-intestinal disturbances, is as yet available.

Metaphen, an organic mercurial, was elaborated by Dr George W Raiziss^{2,3} after an extensive study of chemical compounds involving the nitro-benzene-mercury complex. Metaphen, which is 4-nitro-anhydro-hydroxy-mercury-ortho-cresol, possesses, according to Dr Raiziss, greater germicidal properties than mercuric chloride and many other antiseptics, being especially destructive for staphylococci and other bacteria of the same group, its bactericidal effect on other microorganisms is also very high. This is especially true of spore-bearing bacilli, such as *bacillus subtilis* and anthrax.

Recently, Konrad E. Birkhaug⁴ also studied the bactericidal and bacteriostatic properties of metaphen, which was found by him to possess unusual disinfecting and antiseptic powers far in excess of mercuric chloride and other commonly used antiseptics. When *staphylococcus aureus* was used as the test organism, metaphen had a phenol coefficient of 1,500. Metaphen

was 400 times more efficient than mercurochrome against *staphylococcus aureus* when dissolved in equal parts of human serum and broth. It inhibits the growth of *staphylococcus aureus* after 48 hours incubation in a dilution of 1:16,400,000 while mercuric chloride accomplishes the same in a dilution of 1:32,000. The action of most antiseptics is greatly diminished in the presence of proteins. Hirschfelder and Wright⁷ made an excellent study of the colloid chemistry of antiseptics and chemotherapy, and the effect of certain antiseptics upon proteins. In this study, the authors state

"Metaphen did not produce any noticeable changes in the ultramicroscopic appearance either of egg albumin or plasma, presumably because it has but little affinity for the plasma proteins."

The following table indicates that the toxicity of metaphen is comparatively low when given per os. The rabbit has tolerated from 15 to 30 cc of a 1:1,000 solution, so that the average maximum tolerated dose is about 24 cc per kilo of body weight.

The aqueous solution of metaphen, owing to its high bactericidal and bacteriostatic power and the fact that it does not precipitate proteins, has a wide range of application in many branches of medicine, surgery^{6,7,8,9,10,11}, obstetrics, dentistry^{12,13}, otolaryngology^{14,15,16,17}, ophthalmology, urology¹⁸, and blood stream infections¹⁹.

The author's experience of four years in the oral use of metaphen in gastro-intestinal cases, is summarized in the accompanying table, which gives an analysis of 82 cases taken from his records. These comprise 26 examples of gastric, and 56 of duodenal ulcers. Twenty-seven of these have had thorough x-ray studies, many have had test meal and microscopic study of gastric contents to confirm diagnosis.

The table lists each case by initials, giving age, sex, diagnosis, dosage, and comments regarding x-rays, laboratory tests, diets, and the length of time during which gastro-intestinal symptoms were observed, and present condition, January, 1932.

ORAL ADMINISTRATION OF METAPHEN SOLUTION
1:1,000 TO RABBITS

DATE	DOSE PER KILO OF BODY WEIGHT	TOTAL AMOUNT GIVEN**	RESULTS OBTAINED
3-5-24	20 cc*	65.6 cc	Survived
6-9-25	40 cc	98.8 cc	Survived
5-24-26	40 cc	112 cc	Died on 7th day
6-12-26	30 cc	66.6 cc	Survived
1-30-29	20 cc	37 cc	Survived
10-1-29	15 cc	37 cc	Survived
10-1-29	20 cc	40 cc	Survived
10-14-29	25 cc	66 cc	Survived
10-14-29	30 cc	69.0 cc	Survived
2-25-30	25 cc	78 cc	Survived

*1 cc of 1:1,000 solution is equal to 1 mgm. of metaphen.

**Figures in the column indicate amount actually given according to weight of rabbit, slightly rounded off.

The percentage of complete recoveries suggests a possible specific cure for peptic and duodenal ulcers. This will be proved by more extensive studies as other physicians report their observations.

EIGHTY-TWO PATIENTS TREATED WITH METAPHEN

NO	NAME	AGE	SEX	DIAGNOSIS	CLINICAL COMMENT	DAILY DOSE OF METAPHEN 1500	RELIEF NO OF DAYS	DISCHARGED
1	B A B	44	M	Duodenal ulcer	Intermittent attacks for 20 years	3 cc 2 hr p c	24	R*
2	F G R	40	M	Duodenal ulcer	X-rays 4/23/26, shallow duodenal ulcer, 7/19/26, sub-total gastrectomy, 3/5/27, 2 ulcers on duodenal cap	3 cc 2 hr p c	3	R
3	H R	47	M	Duodenal ulcer	Suffering since Spanish-American War	3 cc 1 hr a c and bedtime	5	R
4	S F M	62	M	Duodenal ulcer	X-rays 3/22/28, very large excavating ulcer in cap	3 cc 2 hr p c	3	R
5	C H M	40	F	Gastric ulcer	X-rays 1928, ulcer lesser curvature of stomach	3 cc ½ hr a c	3	R
6	W H D	60	M	Gastric ulcer	Blood pressure 214/120 Ulcer many years	3 cc 1 hr a c	3	R
7	W S	43	M	Gastric ulcer	Test meal showed gastric ulcer	3 cc 1 hr a c	7	R
8	R S	27	M	Duodenal ulcer	Ulcer several months	3 cc 1 hr a c	3	R
9	V T	31	F	Duodenal ulcer	X-rays positive	13 cc 2 hr p c and bedtime	3	R
10	B C	39	F	Duodenal ulcer	Typical symptoms Exam positive	3 cc 2 hr p c	3	R
11	W S H	55	M	Gastric ulcer	X-rays ulcer lesser curvature, size of a quarter Test meal R B C S	3 cc ½ hr p c and bedtime	3	R
12	W C	56	F	Gastric ulcer	X-rays, 1928 ulcer lesser curvature	3 cc p c and bedtime	3	R
13	J V B	52	M	Gastric ulcer	Many years typical symptoms	3 cc p c and bedtime	2	R
14	W W S	65	M	Duodenal ulcer	Definite symptoms and signs	3 cc 2 hr p c	4	T*

*R=Recovered

*T=Temporary

NO	NAME	AGE	SEX	DIAGNOSIS	CLINICAL COMMENT	DAILY DOSE OF METAPIEN 1 500	RELIEF NO OF DAYS	DISCHARGED
15	C N W	50	F	Gastric ulcer	History of infection of foot	3 cc p c	50	R
16	W H C	51	F	Duodenal ulcer	Typical symptoms Marked secondary anemia	4 cc 2 hr p c	7	R
17	F F	61	F	Duodenal ulcer	Intermittent positive signs for many years	4 cc 2 hr p c	3	R
18	W H C	51	M	Duodenal ulcer	X-rays negative All symptoms positive	4 cc 2 hr p c	13	R
19	P D V N	43	M	Duodenal ulcer	Definite symptomatic diagnosis	4 cc 2 hr p c	20	R
20	W E T	24	F	Gastric ulcer	X-rays Symptoms not relieved by Sippy diet	4 cc $\frac{1}{2}$ hr a c	7	R
21	E M	32	M	Gastric ulcer	X-rays positive	4 cc t i d p c	3	R
22	J H C	45	M	Gastric ulcer	X-rays positive Sippy diet over long period of no avail	4 cc t i d p c	3	R
23	R W A	45	F	Duodenal ulcer	Frequent vomiting several hours after each meal Symptoms positive	2 cc t i d p c	5	R
24	M B M	36	M	Gastric ulcer	Ulcer since World War	4 cc t i d p c	3	R
25	R F F	57	F	Duodenal ulcer	X-ray positive, 1928	4 cc 2 hr p c	7	R
26	D H	19	F	Duodenal ulcer	X-rays positive	3 cc 2 hr p c	14	R
27	P E A	39	M	Duodenal ulcer	X-rays positive, 7/19/29, negative, July, 1930	4 cc 2 hr p c	3	R
28	L B W	53	M	Duodenal ulcer	X-rays positive, 1928, negative, 1931	4 cc 2 hr p c	3	R
29	A S	25	F	Gastric ulcer	Test meal positive	4 cc. with meals	3	R
30	R W.	33	M	Duodenal ulcer	X-rays, 4/15/22, posi- tive Vomiting 2 hrs after meals	2 cc 2 hr p c and bedtime	3	R
31	J P	37	M	Duodenal ulcer	X-rays positive Vom- iting everything, even water	4 cc on rising 2 hr p c	4	R
32	F I	57	M	Duodenal ulcer	Years of distress three hours after eating	4 cc 2 hr p c	3	P

NO	NAME	AGE	SEX	DIAGNOSIS	CLINICAL COMMENT	DAILY DOSE OF METAPHEN 1 500	RELIEF NO OF DAYS	DISCHARGED
33	G Z	41	F	Duodenal ulcer	1½ years Pain three hours after eating	4 cc 2 hr p c	1	R
34	R E V B	24	M	Duodenal ulcer	Ulcer for 8 months Loss of weight	4 cc 2 hr p c	2	R
35	J A	34	M	Gastric ulcer	X-rays negative excepting for spastic colitis Constant nausea and pain immediately after meals	4 cc p c and bedtime	3	R
36	E L D	62	F	Duodenal ulcer	X-rays cholecystitis and chronic colitis, 1924	4 cc 2 hr p c	3	R
37	M H	59	F	Gastric ulcer	X-rays positive Lesser curvature Sippy diet three weeks	4 cc 2 hr p c	4	R
38	E C	45	M	Gastric ulcer	Gastrectomy years ago X-rays, 1929 large ulcer greater curvature of stomach X-rays, 1931, negative	4 cc	3	R
39	B W	34	F	Gastric ulcer	Vomiting immediately after meals for hours	1 cc 2 hr p c	3	R
40	C H	39	M	Duodenal ulcer	10 years typical symptoms	4 cc 1 hr p c	6	R
41	J J	32	F	Duodenal ulcer	Typical symptoms	1 cc 1 hr a c	2	R
42	B J G	32	F	Gastric ulcer	Operated soon for a gangrenous appendix Ulcer cleared up	4 cc 2 hr p c	None	U*
43	J A V	47	M	Duodenal ulcer	Distress 3 or 4 hours for years	4 cc 2 hr p c	3	R
44	J H	20	M	Duodenal ulcer	Pain after each meal	4 cc 2 hr a c	7	R
45	J H T	73	M	Duodenal ulcer	Typical signs for many years	4 cc 2 hr p c	3	R
46	A C	44	F	Gastric ulcer	Typical symptoms with vomiting	2 cc 1 hr p c	5	R
47	A M S	89	F	Duodenal ulcer	Typical symptoms 2 years with great loss of weight	1 cc 2 hr p c	3	R
48	M O J	43	M	Gastric ulcer	Typical signs with loss of weight 3 years	4 cc 1 hr a c	3	R

*U=Unimproved

NO	NAME	AGE	SEX	DIAGNOSIS	CLINICAL COMMENT	DAILY DOSE OF METAPHEN 1 500	RELIEF NO OF DAYS	DISCHARGE
49	CH	37	M	Duodenal ulcer	Typical signs	4 cc. 1 hr p c	3	R
50	FM	58	M	Gastric ulcer	Typical signs with great loss of weight	4 cc	3	R
51	LB	45	M	Gastric ulcer	4 years pain and pressure after meals	2 cc 15 min a c	3	R
52	LC	41	M	Gastric ulcer	2 years typical symptoms	4 cc ½ hr a c	3	R
53	MGB	36	F	Gastric ulcer	X-rays positive	4 cc 2 hr p c	9	R
54	MB	51	F	Gastric ulcer	X-rays positive, 1928 Test meal positive Vomited about 1 oz of blood after meals	4 cc 15 min a c	3	R
55	HLC	38	F	Duodenal ulcer	X-rays positive 1 year with great loss of weight	2 cc 2 hr p c	2	R
56	ECS	51	F	Duodenal ulcer	Positive signs for many years	4 cc 1 hr a c	3	R
57	JAS	51	M	Duodenal ulcer	7 years immediate relief	1 cc 2 hr p c	42	R
58	LSVZ	45	F	Duodenal ulcer	Several abdominal operations without relief	2 cc 1 hr a c	3	R
59	JS	42	M	Duodenal ulcer	Typical symptoms for 3 years with great loss of weight	4 cc 2 hr p c and bedtime	3	R
60	AR	67	F	Duodenal ulcer	Positive signs since 1922	2 cc 2 hr p c	10	R
61	SC.	72	F	Duodenal ulcer	Living on modified Sippy diet for many years	2 cc 2 hr p c	3	R
62	JFJ	25	M	Duodenal ulcer	Typical symptoms for 2 years	4 cc 2 hr, p c	3	R
63	WT	24	M	Duodenal ulcer	Typical symptoms	4 cc 2 hr p c	3	R
64	JAS	48	F	Duodenal ulcer	On modified Sippy diet for 6 months	2 cc 2 hr p c and bedtime	3	R
65	PM.	33	M	Duodenal ulcer	Typical symptoms	4 cc 2 hr and bedtime	1	P
66	RHC	70	F	Gastric ulcer	Diarrhea caused by each meal	4 cc 15 min a c and bedtime	5	P

NO	NAME	AGE	SEX	DIAGNOSIS	CLINICAL COMMENT	DAILY DOSE OF METAPHEN 1 500	RELIEF NO OF DAYS	DISCHARGED
67	D H F	45	F	Duodenal ulcer	Distress 4 hours after eating	4 cc 2 hr p c	3	R
68	S R	61	M	Duodenal ulcer	Coal tar stools since 1900	4 cc 2 hr p c	5	R
69	W H T	50	M	Duodenal ulcer	Typical distress	4 cc 1 hr p c and bedtime	3	R
70	J S	36	M	Duodenal ulcer	Typical symptoms	4 cc 2 hr p c	1	R
71	K P	61	F	Duodenal ulcer	X-ray positive	2 cc 2 hr p c	3	R
72	E S	40	F	Gastric ulcer	Has had 4 major abdominal operations with no relief	4 cc 2 hr p c and bedtime	1	R
73	F P K	42	M	Duodenal ulcer	Pain 4 hrs after eating for years	4 cc 2 hr p c and bedtime	1	R
74	R S C	44	M	Duodenal ulcer	Typical pains 1 year	4 cc 2 hr p c and bedtime	3	R
75	C H C	55	M	Duodenal ulcer	Pain 4 hr p c and 2 A M	4 cc a c and bedtime	3	R
76	A L M	72	M	Duodenal ulcer	Pain 3 or 4 hr p c and 1 A M	4 cc 2 hr p c	1	R
77	G B	73	F	Duodenal ulcer	X-rays show 2 ulcers in bulb	4 cc 2 hr p c	1	R
78	J D	48	M	Duodenal ulcer	Chronic alcoholic	4 cc 2 hr p c	1	R
79	S VanB	44	M	Duodenal ulcer	1 year pain 3 or 4 hr p c	4 cc 2 hr p c	3	R
80	E C B	61	M	Duodenal ulcer	X-rays positive, also spastic colitis	2 cc 2 hr p c	3	I*
81	H B	35	F	Duodenal ulcer	X-rays positive Vom-its even water	4 cc 2 hr p c	1	R
82	I S	51	M	Duodenal ulcer	Pain 2 to 4 hr p c	4 cc 2 hr p c	1	R

*I=Improved

In searching for the fate of the metaphen taken orally, the laboratory has found large traces of mercury in the stool, but none whatsoever in the urine or blood

Toxicity of any type has in no case been demonstrated, and the author has had many patients who have continued metaphen at the dosage of 16 c c daily for months without reporting to him—patients who felt so well that they were afraid to discontinue treatment for fear of recurrence of gastro-intestinal disorders

In 1929, the author increased the dose to 4 c c three times a day, and since then no further increase has been necessary to obtain relief from either pain, pressure or other distress in the abdomen due to gastric ulcer, duodenal ulcer, chronic ulcerative colitis, or other types of colitis. About half of his patients have taken the prescribed dose of the 1:500 solution of metaphen diluted with equal parts of either glycerin or cinnamon water in half a glass of water directly before or after meals in cases of gastric ulcer, or one hour before or two hours after meals in cases of duodenal ulcer. In colitis, metaphen has been given directly after each meal and at bedtime in order that the drug might be carried throughout the intestines along with the food.

In practically all his cases there has been relief from pain in three days' time on the average, regardless of the fact that most of the patients have suffered for years. Many have come to him with the diagnosis of nervous dyspepsia vomiting everything taken by mouth even water. The metaphen solution, however, was never vomited,

and in one to three days the patients were able to eat large meals.

Usually when all pain or distress is relieved in the three day period, the author continues with three or four doses daily for one week, two doses daily the second week, one dose daily the third week, and then a dose every other day the fourth week, stopping the drug thereafter. It is interesting to note the large proportion of these cases, which have had no recurrence of their chronic gastro-intestinal symptoms since their treatment. Their nervous and mental symptoms have disappeared entirely and they have become readjusted to their environment.

X-rays taken before and after the oral administration of metaphen, have shown complete disappearance of the ulcers of the gastric and duodenal types. Chronic ulcerative colitis cases have become symptom-free in a very short time. Diarrheal stools, containing pus and blood, have ceased after the first day.

Most of these cases of ulcers had been on a strict Sippy diet or modified forms of it, and, in every case, the patients have been placed upon a varied diet, nevertheless, there has been no complaint or resulting pain or pressure.

It must be continually borne in mind that all of these cases involved psychoneurosis, either plainly hysterical in type or they were suffering from anxiety or compulsion forms of neurosis. The psychoneurosis has apparently subsided as a result of the direct attack of metaphen upon the gastro-intestinal lesions.

A few of the more striking cases are now described.

CASE REPORTS

Case No I Miss E C, age 45, a clerk in a very responsible position Chief complaint distress in the entire abdomen

Appetite poor Bowels constipated No sleep without sedatives Suffering from a complete nervous breakdown since March, 1930, when her mother died suddenly in her arms Came under the author's care after three months' treatment in a private clinic in a neurological institution In 1905 both ovaries were operated upon for cysts In 1914 she had four operations the first was a gastro-enterostomy on account of gastric ulcers, the other three eventually resulted in a gastrectomy removing four-fifths of the stomach At age 38 she experienced her menopause

On July 7, 1930, a gastro-intestinal x-ray series showed another ulcer on the small remaining portion of the stomach She was still suffering from psychoneurosis She was given metaphen solution 1 500, 4 cc one hour before meals and at bedtime, diluted in an equal amount of glycerin In three days the distress in the epigastrium had entirely disappeared, and in nine days she had gained seven pounds in weight

X-rays of the stomach, April 6, 1931, showed no sign of peptic ulcer She returned to work September 2, 1931, and has not lost any more time She has never had any return of the epigastric pain Her nervous condition has entirely disappeared

Case No II E B W, male, age 53, occupation, proprietor of laundry Chief complaint, distress in epigastrium two hours after each meal

He was a case of profound psychoneurosis On April 24, 1930 he was given 4 cc of the solution of metaphen, 1 500, with an equal amount of glycerin two hours after meals In three days there was no more distress, and he felt like a new man April 29, 1930, the dose of metaphen was reduced to 2 cc X-rays of his gastro-intestinal tract taken in 1928 in October, 1929, and March 1930, all showed ulcer of the bulb of the duodenum X-rays taken June 27, 1930, showed the ulcer greatly improved The x-ray report dated June 27, 1930, was as follows

"Duodenum First portion is fairly large and at times filled completely, with a normal outline, at other times there was a tendency to trefoil deformity Comparing these with previous radiographs made in March, this year, elsewhere, we find that the duodenal cap at this time fills decidedly better and that the deformity noted on the mesial aspect has practically entirely disappeared The deformity noted in prepyloric ulcer is generally organic The deformity noted in postpyloric or duodenal ulcer is generally due to spasm unless a niche or accessory pocket is found We note that at the previous examination in March, the doctor reports that the duodenal cap was not unduly tender on pressure At this time we do not find any marked tenderness, but there is definite tenderness noted over the duodenal cap that is not found elsewhere However, we feel that so far as the deformity of the cap, which is the result of spasticity, is concerned there is definite improvement between March and the present time"

X-rays made in April, 1931, showed no lesion of the stomach or duodenum, and his psychoneurosis had been cured

Case No III P E A, male, age 39, occupation, certified public accountant Chief complaint, complete nervous breakdown This patient has not worked for three years, and complains of distress two to four hours after each meal X-rays, July 19, 1929, showed ulcer of the duodenal bulb He was given 4 cc of metaphen solution, 1 500, with equal amounts of glycerin two hours after meals and in three days the epigastric distress was entirely gone He returned to work immediately and has continued to be employed without interruption to date X-rays taken in July 1930, showed no evidence of duodenal ulcer His psychoneurosis disappeared with the cessation of epigastric distress

Case No IV Mrs W C age 56 occupation, advertising manager of a department store Chief complaint vomiting after meals and nine hemorrhages from the bowels shown by profuse coal tar stools since October, 1927 January 31 1929 she was in a state of profound psychoneurosis X-rays of the gastro-intestinal tract in March 1928 dem-

onstrated an ulcer of the lesser curvature of the stomach. February 11, 1929, she began to take metaphen solution, 1.500, 3 cc in cinnamon water immediately after meals and at bedtime. In three days the gastric distress, vomiting, and symptoms of psychoneurosis disappeared. On March 11, 1929, she was able to stop metaphen and has had no need of any medication whatever to date.

Case No IV W S H, male, age 55, occupation, sales manager, constantly travelling throughout the United States. Chief complaint, constant pain in epigastrium aggravated by food. This patient was profoundly neurasthenic, introspective and apprehensive. X-rays, December 18, 1928, demonstrated an ulcer the size of a twenty-five cent piece on the lesser curvature of the stomach. Gastric analysis showed red blood cells in all tests, normal otherwise. He was placed upon metaphen solution, 1.500, 3 cc in cinnamon water one-half hour after meals and at bedtime, and his report on the third day was that he was entirely relieved of distress after eating. His psychoneurosis has disappeared and he has never had any return of the gastric distress to date.

Case No VI S F M, male, age 62, occupation, retired. Chief complaint, vomiting attacks two hours after eating, loss of weight, and great nervousness. X-rays, March 22, 1928, showed a large penetrating ulcer in the duodenal bulb. He was given 3 cc of metaphen solution, 1.500, diluted in water two hours after meals, and his report on the third day was that he had not vomited since he began taking the metaphen. His nervousness was rapidly improving.

Frequent reports to date (October 1, 1931) are of no recurrence of any signs of ulcer, and he has been absolutely well with no need of any medication whatsoever after the first month.

It now becomes of interest to consider the possible explanation of the beneficent action of metaphen, primarily a bactericidal agent on gastro-intestinal ulcers. In this connection, it must be pointed out that recently the

thesis has been sustained by several authors, that infection plays an important rôle in the evolution of many such ulcers. Extensive investigations in this direction have been carried out by Rosenow^{20,21,22,23}, who was able to demonstrate the presence of streptococci in several cases of duodenal and gastric ulcer. By injection of these organisms into dogs and rabbits he obtained ulcers resembling those in man in respect to location, gross microscopic appearance and in the tendency to become chronic, to perforate, and to cause severe and fatal hemorrhages. The same organism was isolated by him from ulcers in the hog, calf, cow, sheep and dog. These experiments were repeated by Celler and Thalhimer²⁴ who found that non-hemolytic streptococci are present in practically all gastric ulcers; these authors, however, do not regard this as proof that this organism is the factor which either initiates the ulceration or prevents healing; but the constant presence of streptococci in such lesions must have some significance which requires further elucidation.

A similar opinion is expressed by Duval and his co-workers^{25,26}, who ascribe to infection a secondary if not a primary rôle in the development of gastric ulcers. This view is supported by the following facts. While ulcers are usually regarded as evolving without fever, actually a subfebrile state or even an acute elevation of temperature will often appear during a gastric attack; the development of ulcers appears to be influenced by some epidemics and ulcers are frequently aggravated as a consequence of intercurrent infectious diseases. Hyper-

leucocytosis is often observed in patients afflicted with ulcer, thus, Girault²⁶ has found the number of leucocytes above normal in 23 out of 28 patients with ulcer confirmed by operation. Duval has found the intradermoreaction with streptococcus positive in 60 per cent of cases, while the number of leucocytes was above normal in 33 per cent of cases. Furthermore, inflammatory exacerbations in chronic ulcers, and the presence of bacteria in the wall of the ulcer, support Duval's thesis. Of interest is the fact that mortality following large excisions is less than that following small excisions. This apparently paradoxical fact seems to indicate the possibility that the small excision is within an infected zone.

Askanazy²⁷ has found the organism of thrush (*Oidium albicans*) in the tissues of operated gastric ulcers in 25 out of 30 cases. He has also succeeded in creating ulcers experimentally by the inoculation of animals with impaired mucous membrane of the stomach with this organism.

Smithies²⁸ in a study of the etiological factors associated with chronic gastric ulcer, has found that 137 out of 522 histologically proved ulcers, or 33.7 per cent, were associated with an infection.

It thus seems very probable that infection plays an important part in gastro-intestinal ulcer, and it is there-

fore not entirely irrational to expect that a strong bactericidal agent, which is at the same time non-injurious to the tissues in the solutions used should exercise a healing effect on ulcers. The patients' histories, here presented, show that such is the case.

CONCLUSIONS

1 Metaphen, in 1:500 solution, was given orally to patients with symptoms of chronic abdominal distress in the dose of 4 c.c. three times a day with very gratifying results.

2 The material presented includes an analysis of 82 cases, 26 of gastric and 56 of duodenal ulcers. Complete x-ray studies were made of 27 of these cases, diagnosis was also confirmed in many cases by test meal and microscopic study of gastric contents.

3 Relief from pain was obtained in practically all cases in an average of three days' time.

4 No toxic effects were ever observed.

5 Complete disappearance of gastric and duodenal ulcers consequent upon treatment with metaphen has been demonstrated by means of x-ray studies, made before and after treatment.

6 A possible explanation of the action of metaphen, primarily a bactericidal agent, may lie in the part played by infection in the evolution of ulcers of the type considered, as has been recently emphasized by several authors.

REFERENCES

- ¹AARON, C. D. Diseases of the digestive organs with special reference to their diagnosis and treatment, 1918, Lea & Febiger, Philadelphia, 448.
²RAIZISS, G. W., and SEVERAC, M. A new organic mercury compound with power-

- ful germicidal properties, Jr. Lab and Clin Med, 1923, 18, 71-80.
³RAIZISS, G. W., and SEVERAC, M. Metaphen (4-nitro-3, 5-bisacetoxymercuri-2-cresol) and its bactericidal properties, Jr. Infect Dis, 1927, 31, 447-452.

- ⁴BIRKHALG, K E Metaphen (4-nitro-3, 5-biacetoxymercuri-2-cresol), comparative study of commonly used disinfectants and antiseptics, histologic changes produced by intravenous administration of metaphen in rabbits, Jr Am Med Assoc, 1930, xcvi, 917-923
- ⁵HIRSCHFELDER, A D, and WRIGHT, H N Studies on colloid chemistry of antiseptics and chemotherapy, ultramicroscopic examination of neoarsphenamine and of certain antiseptics, and their effects upon protein solutions Jr Pharmacol and Exper Therap, 1930, cxlix, 13-27
- ⁶YORK, D A First aid and after treatment of minor injuries, Texas State Jr Med, 1927, xlii, 709-710
- ⁷THORPE, M The etiology, prevention and treatment of post-operative wound infections, Ill Med Jr, 1926, 1, 477-483
- ⁸BLEDSOE, R E B Metaphen locally and intravenously Jr Chemotherapy, 1928, v, no 1, 37
- ⁹FISK, S Metaphen in streptococcic lymphangitis and adenitis (a case report), Clin Med and Surg, 1927, xxxiv, 378-379.
- ¹⁰SPOTTS, S D Metaphen in treatment of peritonitis, Jr Chemotherapy 1927 iv, no 2, 48-50
- ¹¹FISHER R Ruptured appendix and peritonitis treated with metaphen (a case report), Clin Med and Surg, 1927, xxxiv, 857-858
- ¹²JAMES, F The etiology and treatment of Vincent's angina, Jr Chemotherapy 1929 vi no 1, 4-8, and no 3 9
- ¹³SYMON, W G Metaphen in the treatment of Vincent's angina Clin Med and Surg, 1931, xxxviii 825-826
- ¹⁴BROWN, I C Metaphen in the prevention and treatment of colds, Clin Med 1925, xxxii 181
- ¹⁵SCHLESKY, E C The treatment and prevention of colds with metaphen Clin Med 1925, xxxii 150-151.
- ¹⁶LEWIS, R A Dye stuff antiseptics in otitis media, Ann Otol Rhin and Laryngol 1925, xxxiv 881-886
- ¹⁷GORMAN, J R Non-operative treatment of chronic otitis media suppurativa, Virginia Med Monthly, 1926, liii, 378-382
- ¹⁸DUBOIS, L C Acute prostatitis—a new conception of its etiology and treatment, Clin Med and Surg, 1928 xxxv, 331-332
- ¹⁹BERNSTINE, J B Metaphen in the treatment of puerperal septicemia and other blood stream infections, Am Jr Obst and Gynec, 1929, xliii, 220-229
- ²⁰ROSENOW, E C The production of ulcer of the stomach by injection of streptococci, Jr Am Med Assoc, 1913, lxi, 1947-1950
- ²¹ROSENOW, E C Relation of and the lesion produced by various forms of streptococci with special reference to arthritis, Jr Am Med Assoc, 1913, lxi, 2007
- ²²ROSENOW, E C The causation of gastric and duodenal ulcers, by streptococci, Jr Infect Dis, 1916, xix, 333-362
- ²³ROSENOW, E C, Etiology of spontaneous ulcer of stomach in domestic animals Jr Infect Dis, 1923, xxxii, 384-399
- ²⁴CILLER, H L, and THALIMIER, W Bacteriological and experimental studies on gastric ulcer, Jr Exper Med, 1916, xxxiii, 791-812
- ²⁵DUVAL, P Note sur la role de l'infection dans l'evolution des ulcres gastro-duodenaux et sur les indication therapeutiques qui peuvent en resulter, l'Acad de med, 1924, xcii, 1257-1259
- ²⁶DUVAL, P, ROUX, J C, and MORIET, F Rôle de l'infection dans l'evolution des ulcres gastro-duodenaux indications therapeutiques Presse med, 1925, xxxiii 3
- ²⁷ASKANAZY, M Über Bau und Entstehung des chron Magengeschwurs sowie Scorpilbefund in ihm, Virchow's Arch path Anat, 1921, cxxxiv, 111-178
- ²⁸SMITH, F Observations upon the nature, diagnosis and clinical management of gastric ulcers with suggestions for ratio of regimen of treatment, Am Jr Med Sci, 1923, clxxvi 781-801

The Rôle of the Bowel in Chronic Arthritis

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THE bowel is usually mentioned as a possible origin of the varied nerve, muscle, and joint syndromes characterizing chronic infectious or atrophic (American Committee for the Control of Rheumatism) arthritis. The colon has been taken to be a focus of infection, the source of bacterial toxins or the seat of auto-intoxication. Free action of the bowels has always been advocated in the treatment of arthritis. Numerous medicinal and mechanical measures have been elaborated to secure this. The adnexa of the bowel, the appendix and gall-bladder, have played prominent rôles as possible foci of infection. Fletcher and Graham¹ found the colon in chronic arthritis characteristically atonic.

The varied and varying flora of the bowel has been repeatedly studied in its relation to arthritis. Burbank,² Keating³ and Crowe⁴ have reported success in using vaccines of fecal organisms in the treatment of chronic arthritis.

Traut and Herrold⁵ found streptococci much more commonly on the rectal mucosa of arthritic patients than in the rectums of controls. Since then the rectal flora of many more patients has been studied. The later results

tally with those already reported. Streptococci, usually green, less commonly hemolytic, are found far more commonly in the rectums of arthritic patients than in normal controls and often are the predominating organisms in cultures made by our method (Table I). This method has been a great improvement over previous means of isolating bacteria not included in the bacterial population of normal individuals, the bacteria peculiar to the arthritic. The usual stool culture selects material from the bowel lumen or stool center, a medium unfavorable to the growth of a delicate streptococcus because of competitive bacteria, presence of bacteriostatic substances and lack of water.

Repeated cultures of the rectal wall have usually shown similar floras. To some extent the kinds of bacteria and their relative proportions have fluctuated with exacerbations and remissions of the patient's joint or gastrointestinal symptoms. Frequently I was able to confirm the opinion that with looser stools there was a higher percentage of streptococci. In some rectums staphylococci have been especially numerous. They are usually white staphylococci. Checks of our method have failed to demonstrate skin contaminations. As will be shown later many of these staphylococci are agglutinated strongly by serum from

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NO OF PT	SEX	AGE	SEVERITY	STREPTOCOCCI	PER CENT OF STREP-TOCOC-CI	OTHER BACTERIA	GASTRO-INTESTINAL STATUS AND REMARKS
1	F	32	I	None	5 to 90	B coli	Normal digestion
2	F	43	III	Green	60	B coli	Pulmonary tuberculosis
3	M	33	I	"	20	Staph albus	Alternating diarrhea and constipation
4	F	27	I	"	15	B coli	Constipation
5	F	32	I	Hemolytic	5 to 30	B coli	Spastic colitis
6	F	48	II	Green	5	B coli	Spastic colitis
7	F	48	I	"	5	B coli	Fermentative colitis
				Indifferent	5	Staph albus	Irritable bowel
8	F	80	II	Green	10	5%	Constipation
9	F	44	I	"	20	B coli	Cathartic colitis
10	F	46	I	"	10	B coli	Constipation
11	M	35	I	"	10	B coli	Constipation
12	F	46	I	"	10	B coli	Constipation
13	F	45	I	"	2	B coli	Irritable bowel
					2 to 80	Staph albus	Rheumatic purpura
14	F	50	II	"	10	10%	Ptoisis
15	F	58	III	Indifferent	7	B coli	Severe irritable bowel
16	F	47	II	Green	3	B coli	Fermentative colitis
17	F	72	III	Hemolytic	50	B coli	Unknown
18	F	48	I	None	10	B coli	Constipation
19	F	52	I	Green	50	B coli hem	Ptoisis
20	M	27	I	"	10	10%	Irritable bowel
21	F	25	I	"	2	B coli	Normal
22	M	46	II	"	10	B coli	Normal
23	F	47	I	Hemolytic	5	B coli	Normal
24	F	56	I	Green	50	B coli	Constipation
25	F	58	III	None	10	Staphy 30%	Ptoisis
26	F	55	II	Green	2	B coli	Inactive case with anchyloses
27	F	54	II	"	2	B coli	Ptoisis
28	M	29	I	None	10	B coli	Constipation
29	F	68	II	Green	2	B coli	Irritable bowel
30	F	42	I	Hemolytic	10	B coli	Constipation
31	M	32	I	Green	50	Staphy 25%	Chronic proctitis
32	F	50	I	Hemolytic	30	B coli	Strept virid obtained
33	M	45	III	None	33	Staphy 30%	Chronic cholecystitis
34	F	24	II	Green	1	B coli	Chronic appendicitis
35	F	54	I	"	2	B coli	Green streptococcus found after one month
36	F	24	I	"	2	B coli	Hemolytic absent

NO OF PT	SEX	AGE	SEVERITY	STREPTOCOCCI	PER CENT OF STREP- TOCOC- CI	OTHER BACTERIA	GASTRO- INTESTINAL STATUS AND REMARKS
37	F	37	I	"	4	B coli	Irritable bowel
38	F	50	II	"	40	B coli	Irritable bowel Hyperthyroidism
39	F	68	III	None		B coli	Irritable bowel Constipation
40	M	42	I	Green	10	B coli	Ptosis
41	F	60	I	"	2	B coli	Constipation Constipation
42	F	64	II	"	50	B coli	Irritable bowel
43	F	22	IV	"	30	B coli	Irritable bowel
44	F	34	II	"	5	B coli	Irritable bowel
45	M	37	I	Indifferent	10	Staphy 50%	Spastic colitis Atonic ptosed colon
46	F	25	II	Green	50	B coli	Pulmonary tuberculosis Chronic prostatitis Green streptococci found
47	M	35	I	None		B coli B coli	Hypothyroidism
48	F	60	I	Green	30	Staph albus 10%	Constipation
49	F	58	II	Hemolytic	2	B coli	Peptic ulcer
50	F	45	II	Green	5	B coli	Irritable colon Irritable bowel
51	M	43	I	Green	15	B coli 85%	None
52	M	46	I	Indifferent	1	B coli	Mucous colitis
53	M	47	II	Hemolytic	80	B coli 15%	Constipation
54	F	53	I	Green	80	Staph albus 5%	
55	F	47		"		B coli	Constipation
56	F	22	IV	"	2	B coli	Normal
57		47	I	"	50	B coli	Constipation
58	F	62	I	"	1	B coli	Constipation
59	F	22	I	"	2	B coli	Constipation
60	M	37	III	"	50	B coli	Constipation

arthritic patients. Vaccines made from them have acted as powerful antigens aiding the patients in recovery. Crowe has also isolated his "*micrococcus deformans*", a white staphylococcus, from the stool.

The percentage of streptococci in the rectum bore no relation to the severity of the disease. Neither was the type of streptococci related to the variety or severity of joint disease except in one instance. In one case of rheumatic fever indifferent streptococci were repeatedly isolated from the rectum. The rectum of a patient with rheumatic purpura yielded five per

cent to ten per cent of green streptococci on two examinations. Streptococci were rarely found in the rectums of patients with osteo-arthritis.

Other workers, as well as I, have found the streptococci of the mouth and teeth very similar, if not indistinguishable from the streptococci of the bowel. It is presumable that pathogenic bacteria resident in the mouth or ingested in food passing the more or less efficient and variable barrier of the bactericidal stomach secretions should enter the bowel unscathed. The bowel stasis described as characteristic of the entire gastro-intestinal tract by

Fletcher and Pemberton, would favor their absorption or the absorption of their toxic products. Arnold⁶ has found *B. prodigiosus* in the blood after feeding it to guinea pigs. The subsequent involvement of joint or other tissues is a direct consequence. Redewill, Potter and Garrison⁷ mention the migration of streptococci from the bowel to teeth and tonsils.

The remarkable frequency of gastro-intestinal symptoms and findings in patients with atrophic arthritis stimulated me to investigate the relation of the gastro-intestinal disorders to joint disease. Care was taken to separate such localized diseases as cholecystitis or appendicitis. In most of the patients, abdominal symptoms were those commonly ascribed to irritable bowel, mucous or spastic colitis. Almost all had some intolerance to starch. Their digestive disturbances were much improved by reducing the gross starch of their diets. Fermentative colitis and its possible relation to Pemberton's disturbed carbohydrate utilization in these patients has recently been described by Monroe and Hall.⁸ Under the fluoroscope the colons of most of these patients were dilated and atonic.

In my patients the gastro-intestinal complaints were so prominent as to demand dietary instruction as one of the very first measures in our broad attack upon the rheumatic disease. The relation between the gastro-intestinal dysfunction and the joint disease was obvious. Exacerbations of joint symptoms were coincident with relapses of the gastro-intestinal disease. The most common relapse was increase in flatulence, constipation and swelling of the abdomen. In some cases the arthritis improved

abdominal pain, flatulence and loose stools. Constipation has been prominent in the complaints of most of my patients. Relief of constipation has always meant substitution of vegetables and fruits for foods of high carbohydrate and caloric value. Improvement has been much more marked by relieving constipation through dietary measures rather than by cathartics.

Seven of the sixty patients cultured showed no streptococci in the rectum. Nos. 28 and 47 had chronic prostatitis. Obvious foci had been removed from the other five patients previous to the rectal cultures. Patients 1, 18, 25, and 28 showed no streptococci on one culture. Patient 33 showed none on two examinations. Possibly further cultures in these cases would have shown streptococci. Patient 25 was a healed case in perfect health except for ankylosis of a hip and the vertebrae. Her active arthritis had terminated more than 15 years before.

The history of patient 13 is interesting. She first consulted me because of purpura. On this occasion no streptococci were obtained from the rectum. Thirteen months later she complained of stiffness of the neck associated with grating in the cervical vertebrae. These vertebrae were definitely tender. Coincidentally streptococci were easily isolated from the rectum.

Hemolytic streptococci were first obtained from the rectum of Mrs. B. She was given five subcutaneous injections of a vaccine of these organisms. After 18 days no hemolytic bacteria were detected. Coincidentally her arthritis had disappeared.

The colon bacilli found have usually been of the non-hemolytic commensal

type In six instances hemolytic colon bacilli were isolated

I have arbitrarily graded chronic arthritis into grades I to IV Grade I comprises those with pain and little deformity or those with deformity of slight degree, not interfering with their occupation Grade II includes those with more marked disability Grade III embraces those with deformity in many joints but still allowing the patient to be about with much discomfort Grade IV includes those completely disabled, the bedridden, and those able to be about only on crutches or in wheel chairs

We have cultured the rectum in fifteen patients free from arthritis Streptococci were found only in a patient with purpura of the rheumatic type, a syndrome allied to arthritis and in two patients with chronic ulcerative colitis Streicher and Kaplan⁹ have called attention to the frequency of streptococci in the colons of patients with ulcerative colitis Cultures were repeatedly made of the nonarthritic patients Those without streptococci in the first examination did not have streptococci in subsequent examinations

Relief of the arthritic symptoms and findings was usually coincident with a reduction of the number of streptococci in the rectum In my opinion the improvement indicated a change in the "soil", a lessened susceptibility to its parasitic flora, as well as a reduction of invading pathogens

Eighty-one per cent of my patients were women and of these seventy-one per cent were between 40 and 60 years of age

In a few instances we encountered

the difficulties in classification of chronic arthritis patients mentioned by Jordan and Boland¹⁰ Whether a patient had a recurrence of rheumatic fever or a flare-up of atrophic (rheumatoid) arthritis was occasionally difficult to ascertain

The streptococci isolated were usually of the viridans type They were usually in short chains All retained the Gram stain They were ovoid to round Usually the individual bacteria were large They frequently appeared in pairs, like an individual coccus or a diplococcus Their broth cultures were diffusely clouded Only rarely was it difficult to grow them in broth Their colonies were originally all "smooth", with evenly round borders Prolonged cultivation brought out dissociation Colonies might not grow so distinctly green, approaching the indifferent or gamma group of Brown

It is impossible to classify my strains of rectal origin according to the plan of Andrews and Horder¹¹ According to them *streptococcus fecalis* ferments the same sugars as does *streptococcus salivarius*, namely, it ferments mannite but does not ferment raffinose or inulin I have found no green streptococci in the bowel fulfilling these requirements The green streptococci found fermenting mannite but not raffinose have also been resistant to bile and heat, placing them in the class of enterococci The *enterococcus* and *streptococcus mitis* (Holman) predominate

The green streptococci isolated from the bowel have usually been of low virulence for animals One cubic centimeter of a 24-hour broth culture injected intraperitoneally does not kill

mice; and even in doses as large as 5 c c, has failed to produce arthritis in rabbits. I discovered that arthritis could occasionally be produced by inoculating the streptococci into the colon. The same strains were without effect on intravenous injection.

Hemolytic streptococci were isolated from the rectums of four patients with atrophic arthritis. According to their fermentative ability they were *Streptococcus hemolyticus* II (Holman), *Streptococcus infrequens*, and *Streptococcus subacidus*. These streptococci have retained their extreme hemolyzing ability over one year of subculturing. Of any of these hemolytic strains, 0.5 c c of a broth culture is fatal to mice in 12 hours. The heart's blood of the dead mice was subcultured on blood agar plates. The washings of one of these plates proved fatal to rabbits in 5 to 14 days. Both purulent and non-purulent arthritis were manifested by these rabbits.

Some strains are conspicuously agglutinated by high dilutions of patient's blood. Extensive agglutination experiments suggest the inter-relationship of these various strains as well as their relation to the disease of their hosts. The isolated streptococci were usually agglutinated by their homologous sera. Certain strains were agglutinated by the sera of other patients in such high dilutions as to suggest an immunological relationship of the rectal streptococci found in arthritics.

TREATMENT

The serum of patients was routinely used in agglutination experiments against significant bacteria isolated from the rectum, from the interior and

exterior of extracted teeth, from prostatic secretions or from the centers of excised tonsils. I included in these agglutinations long-studied strains agglutinated by the sera of other arthritics. I selected such as had proven effective antigens in the vaccine treatment of other patients as judged by the relief of the arthritic symptoms and the disappearance of the arthritic findings. The vaccines used were made of the organisms agglutinated by the patient's serum in high titer. For the most part these were streptococci of rectal origin.

Fifty-eight patients with chronic arthritis were observed sufficiently long to justify an appraisal of their treatment. These patients were followed for three years. Twenty-seven of these patients received no vaccine from me. Thirteen of these non-vaccine patients, or 48 per cent, recovered entirely or were greatly relieved. All of the patients, when first seen, are placed in the non-vaccine group. It is only after their failure to improve upon graded exercise, regulated rest, diet, massage and removal of foci, and after a careful bacteriological and immunological assay that they are subjected to vaccine treatment. Consequently the second group, the vaccine cases, really represent the more difficult patients, those remaining after non-specific measures have failed. Thirty-one patients were treated with vaccine. Twenty-one (68 per cent) of these were markedly improved or recovered. Four had almost no relief. One of these has osteo-arthritis. Osteo-arthritis is not recognized as an infection and is not accessible to treatment by bacterial antigens. Another was

stenographer, badly crippled and terribly fatigued, managing to stay at work. She seemed "burned out", depleted of the elements necessary to recovery. She is now in remission, after cessation of vaccines, upon the institution of rest periods and the postural exercises of Goldthwaite and Osgood. A man, although badly crippled, sold goods from house to house. Like the stenographer, he was continually exhausted, unable to marshal sufficient energy or resistance to fight the disease. Four of the 31 vaccine patients made substantial improvements on subcutaneous administration of a suspension of the *Micrococcus deformans* of Crowe, and casein. Since the sera of these patients did not agglutinate the *Micrococcus deformans*, and no staphylococci were isolated from their foci of infection, improvement of these four patients must be credited to foreign protein.

A solution of casein was often combined with the streptococcus vaccine. Given alone it did not benefit any patient with arthritis. The combination was much more effective than either the streptococcus emulsion or the casein used in much larger amounts separately. Possibly the casein prepared the tissues, increasing their susceptibility to the bacterial antigen. As noted

by Crowe the addition of a staphylococcus to the streptococcus vaccine enhanced its benefits. Crowe ascribes specificity to this staphylococcus effect. Again, a polyvalent vaccine of all the bacteria agglutinated by the patient's serum was successful where an autogenous vaccine failed.

Whether vaccine raises the resistance of the patient or desensitizes him to bacterial allergens, it has an important position in the treatment of chronic arthritis.

SUMMARY

1 Rectal cultures in arthritic patients yielded streptococci more frequently and in larger numbers than did similar cultures in non-arthritics.

2 Streptococci isolated have for the most part belonged to the enterococcus group.

3 Agglutination by the serum of the host and cross-agglutination of other rectal strains are present.

4 Forty-eight per cent of a group of patients with chronic arthritis were markedly improved or recovered with the help of non-specific treatment.

5 Sixty-eight per cent of the patients treated with vaccines of the streptococci from rectal and other foci were markedly improved.

REFERENCES

¹FLETCHER, A. A., and GRAHAM, D. The large bowel in chronic arthritis, *Am Jr Med Sci*, 1930, *CLXXIX*, 91-93.

²BURBANK, R. Vaccine therapy and serological diagnosis in the arthritides, *Jr Bone and Joint Surg*, 1926, *viii*, 657-665.

A study of the streptococcus in the etiology of arthritis, *N Y Acad Med Bull*, 1929, *v*, 176-187.

³KEATING, P. M. Treatment of chronic arthritis with autogenous streptococcus vaccines, *Texas State Jr Med*, 1929, *LXIV*, 691-693.

⁴CROWE, H. W. The specific vaccine treatment of chronic arthritis and rheumatism, *Jr Lab and Clin Med*, 1930, *xv*, 1072-1092.

⁵TRAUT, E. F., and HERROLD, R. D. A simple method of making cultures of

- the rectum, Jr Infect. Dis, 1929, xlv, 172-174
- ⁶NEDZEL, A J, and ARNOLD, L Influence of egg white upon the absorption of bacteria from the intestinal tract, Proc Soc Exper Biol and Med, 1931, xxviii, 358-359
- ⁷REDEWILL, F H, POTTER, J E, and GARRISON, H A Colon as a site of focal infection in chronic pyelitis, cystitis and prostatitis, Jr Am Med Assoc, 1930, xciv, 688-694
- ⁸MONROE, R T, and HALL, F C The feces of patients with chronic arthritis, Arch Int Med, 1931, xlii, 764-770
- ⁹STREICHER, M H, and KAPLAN, B Chronic ulcerative colitis, Jr Am Med Assoc, 1930, xciv, 10-12
- ¹⁰JORDAN, E P, and BOLAND, J P Results of blood cultures in acute polyarthritis, Jr Infect Dis, 1930, xli, 148-151
- ¹¹ANDREWES, F W, and HORDER, T J A study of streptococci pathogenic for man, Lancet, 1906, ii, 708-713

Hygiene of the Soul by Maimonides 1135 to 1204 A.D.

"IT IS known to my lord, may God lengthen his days, that the emotions of the soul bring about great, general, obvious, definite changes in the body. One sees how a person of robust build, sonorous voice, and blooming complexion, when he suddenly receives news that troubles him exceedingly, at once his color becomes pale, his look softens, his posture stoops, his voice becomes weak, and if he should want with all his might to raise his voice, he is unable to do so, his strength weakens. He often trembles on account of weakness, his pulse beat becomes smaller, his eyes sink into their orbits. His eyelids become so heavy that they cannot move, the body surface becomes cold, and his appetite vanishes. The cause of all these phenomena is the withdrawal of the natural heat and blood into the body. The reverse of this is seen in an individual of weak physique, changeable color, and tender voice, as soon as he is met with something that rejoices him a great deal, how his physical strength is increased, his voice raised, the face lit up, his movements become lighter. His pulse beat becomes stronger, his body surface warmer, joy and delight appear so evident that he no longer can conceal it and keep it to himself. All these happenings, the movements of the natural heat and the blood to the periphery of the body, the condition of the body, and the condition of the coward and hopeful as well as that of the indifferent and phlegmatic person are well known, and likewise the conditions of the one in despair as well as of the one conscious of success are clear."

(From a translation by HARRY A. SAVITZ, M.D., in *Annals of Medical History*, 1932, iv, 80-86.)

A Sporadic Benign Rickettsial Fever With Occasional Exanthem

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IN the north temperate latitude, fevers of abrupt onset and intense, short course, but without rash or contagiousness are among the commoner ailments of the summer months. Food or water borne infections cause a goodly proportion of such cases. The respiratory tract infections, exacerbations of chronic intestinal, nasopharyngeal or other focal infections, and the acute pyogenic processes of cryptic location all contribute such a share of cases that by coincidence and concatenation of circumstances they may even give rise at times to the false appearance of a sporadic or epidemic disease being present in a locality. Acute non-exanthematic infections of transmissible nature, such as mild anterior poliomyelitis in sporadic or epidemic form, influenza and other known diseases, such as scarlatina in a very mild form, may also cause a sporadic outbreak the nature of which is not recognized at first, or even throughout its course, provided necessary diagnostic procedures are not carried out.

That the food and water borne infections, endogenous and contact diseases do not, however, account for all sporadic outbreaks in the summer

months of the north temperate latitude may be suspected from our knowledge of the insect borne diseases, such as malaria, typhus fever and dengue of the less temperate climates. It is possible, therefore, that insects are the vectors of some of the acute, prostrating, non-exanthematous fevers of short duration and unknown nature, as observed in the north during the summer months, and called "summer flu" or summer influenza. Whether this sporadic summer disease of the north is in reality influenza or an influenza-like disease, or some quite distinct sort of disease has not been investigated at all, it having been taken too generally for granted that it is "influenza for all practical purposes". While one cannot deny that influenza may occur epidemically, or even sporadically, in the summer months, yet it actually appears that most of the cases of so-called "summer flu" have characteristics by which a careful observer can distinguish them from influenza as it is known in the winter and spring, and in reality throughout the whole year.

The main clinical differences between influenza and the so-called "summer flu" consist in the absence in the latter of lachrymation, coriza (or rhinorrhea) and more or less bron-

chitis, whereas in "summer flu" the fever is higher and steadier, the pulse more rapid and wiry, and in "summer flu" there is greater likelihood of nausea, vomiting and constipation, but less hebetude and drowsiness, the initially keyed-up sensorium of "summer flu" giving place at times to a light delirium. While headache, backache and aches generally are equally common in both diseases, the weariness and malaise of influenza are comparatively more vaguely localized, whereas in "summer flu" they are more apt to be described as neuralgic or rheumatoid pains in definite places, chiefly the neck, back and extremities. One curious minor difference is that the neuralgia of the scalp so commonly encountered in influenza is absent in "summer flu". Finally it may be said, but with less assurance, that the convalescence from "summer flu" is more rapid than from influenza, at least it does not have a sequential nasopharyngeal suppuration as influenza may have.

Surmising from the above facts that "summer flu" may consist in part, at least, of some disease of unknown nature, it has been our object to determine the nature of the disease, its mode of spread, and in whatwise it may be a form of, or else related to, well known diseases that occur elsewhere, particularly in less temperate climates.

The data and conclusions presented herewith are the result of observations extending over a period of six years, and are a development of certain early observations that suggested but did not at once prove that certain spotted and epidemic fevers might follow the

bites of certain blood sucking bugs (hemiptera). A discussion of the cases with exanthem conforming to the spotted fever type or the endemic typhus type, with particular reference to the vectors involved, will be reserved for a subsequent paper. This article will be limited, therefore, to a description of the non-exanthematic, or very usually non-exanthematic fever, that has, in the northern states, added its cases to the medley popularly known as "summer flu". For the sake of preciseness and clarity, the basis for our characterization of this definite entity will be the following presentation of our findings in a definite group of cases studied recently. We were led to investigate this sporadic outbreak on account of our interest in, and in conformity with, conclusions that we had previously deduced from a study of cases in which the element of sporadic outbreak was not so well marked. In general it may be said, however, that our previously recognized isolated cases conformed in clinical course to the disease here described as a typhus-like disease, and that a consideration of them would not alter or add to the characterization of the disease as made out from a study of the sporadic group upon which we base our report, except insofar as to indicate that the non-exanthematic typhus-like disease of the summer months in a temperate climate may occur as isolated cases and may run a somewhat milder course than encountered for the most part in the sporadic outbreak reported in this article.

A systematic description of the disease will be followed by epidemiological

cal notes on the sporadic outbreak that was the source of this material, by case histories of ten of the eleven cases in this group, and by protocols of blood studies on eight of the above mentioned eleven cases. A comparison with the related diseases of the typhus-spotted group will conclude the article.

DESCRIPTION OF THE BENIGN TYPHUS-LIKE DISEASE

Initial bites by insects have been noted in about 80% of the cases. The lesions at the sites of the bites have been small erythematous papules about three millimeters in diameter. The papules have never ulcerated nor commonly shown vesiculation at their apices.

The incubation period varies from ten to fourteen days, being mostly twelve days in duration. Well characterized prodromes do not occur, although a fourth or a third part of those about to take ill notice an unusual sense of fatigue, and a vague malaise for some hours before onset.

Without a preceding subnormal temperature, the onset comes on suddenly (or occasionally subabruptly) with nausea, malaise and a rapid accession of fever. With the rise of the latter there may be a feeling of chilliness, but this is not an outstanding feature of the onset. Rigors occur only very exceptionally. Dull headache, chiefly of a diffuse or vertex type, is complained of by patients during or a little after the onset. Abdominal discomfort, rarely severe, and usually of upper abdominal or diffuse type, develops *pari passu* with nausea and vomiting. The latter usually occurs one or more times, and often

repeatedly, protractedly, and with bilious ejecta.

Neuralgic or rheumatoid pains are not a prominent feature of the disease at onset or latterly, but occur to some extent, being noticed in the cervical and dorsolumbar muscles chiefly, and as cramp-like pains of the extremities, chiefly the lower.

The fever reaches a fastigium (or prefastigium) of 104°F to 105°F within twelve hours, usually rising during the next twenty-four hours (with or without a slight preceding remission) to a perfastigium of 105.5°F to 106°F. The latter temperature, or more usually a degree lower is held with very slight remissions for the next sixty to seventy-two hours thereupon declining by very rapid lysis to normal or near normal, or even subnormal. Sometimes the lysis is not so rapid, the temperature declining consistently at the rate of about two degrees a day for two or three days. A secondary rise will be noticed later.

Both pulse rate and respirations are accelerated, the latter in proportion to the fever, but the pulse, up to 140 or 145 per minute, being for the most part slightly accelerated out of proportion to the temperature, although well sustained, tense and wiry, except in elderly persons.

Toward the end of the first twelve or eighteen hours of fever the face becomes flushed and the conjunctivae become intensely congested, but lachrymation, rhinorrhea, coryza, or turbinal or pharyngeal congestion do not occur at any time. Faucial or tonsillar engorgement is invariably absent, and a subjective sensation of sore throat is

almost never noticed. Cough is infrequent and invariably dry, but most patients cough a little toward the end of the disease.

Constipation is troublesome from the outstart, and throughout the whole course of the disease, often falling but little short of a serious obstipation. The tongue becomes coated with a universal, thin, dry, white fur, but is neither swollen nor shrunken, nor protrudable with difficulty. There is no difficulty in micturation.

The sensorium is clear throughout the first two or three days, sleep being usually troubled, and occasionally somewhat wanting. Delirium, even the mildest, is a quite exceptional occurrence, but has been noticed for brief periods in a few cases. Micropsia was reported in one case. Drowsiness supervenes after the first two or three days (occasionally earlier) but stupor does not occur. Increase of mental and muscular fatigability are noticed toward the end of the disease, but with onset of convalescence the mental and muscular tone improve rapidly, even at a rate greater than the impaired circulatory tone would seem to justify. The moderately impaired circulatory tone and the considerable secondary anemia are the chief features of the latter course of the disease. The appetite returns readily.

A rash is not a frequent phenomenon of the sporadic benign rickettsial disease. It occurred once only in the eleven cases of this epidemic. Preliminary phenomena such as maculopapulous nodules, erythema of the skin, etc., do not occur except that the face is flushed but only the head after the fever reaches the height or is receding.

The rash as observed consisted of a lentil sized, non-confluent, erythematous-macular (deep rose colored) exanthem that appeared three and a half days after onset and was at no time either hemorrhagic or pruritic. It appeared first around the ankles and thence spread up the lower limbs to reach the groins by the end of the first day. The arms broke out not quite a day after the first appearance of the rash, the abdomen, flanks and chest, in order named, being the last parts to become involved. The rash faded quickly with the subsidence of the fever, but came out again less intensely during the secondary rise of the temperature.

A secondary rise of temperature was observed as an unmistakable phenomenon in one-half of the cases, but could be noticed to a slight degree in most of the other cases. In most instances the remission fell to below normal and lasted only a day or a little less, but in one case the remission lasted two days. The secondary rise lasted only one day, and seldom exceeded 101°F . Subsequent remissions of very slight degree were noticed in one or two cases.

In four cases, a blanching of the papules at the site of insect bites was noticed two to four days following the lysis of the fever. It was quite probable that this phenomenon occurred in other cases but failed to be observed. The white spots of the anemic areas lasted two to several days.

EPIDEMIOGRAPHY

In early August of 1932, there occurred in Pittsfield, Illinois, the almost simultaneous appearance of eleven cases of an acute febrile non-exor-

thematous, hyperpyrexial fever of short duration. The known cases of clinically distinguishable character occurred chiefly among a party of boys who visited a natural swimming pool. The latter had long been a resort known favorably for its sanitary character.

On the day of exposure, July 26, the pool was visited by two groups, the boys above mentioned, and a smaller group that did not partake of the same food as the boys, and kept well apart, although not strictly isolated from them. Nine cases developed among twenty-three persons (three adults and twenty children) comprising the boys' group, and one (possibly two) cases developed among five adults and four children comprising the other group. The following day the pool was visited by a small group in nowise in contact with either of the first two groups. In this third group one case developed.

Food could be positively excluded as the source of the infection inasmuch as all twenty-three persons of the first group partook of the same food, but only nine were taken ill. The food consisted of peanut butter and pimento sandwiches, homemade cookies, deviled eggs, and ice cream cones. No water was drunk at the pool or at a farmstead as the meal was eaten in town.

Water of the pool swallowed by the boys while in swimming could not so clearly be excluded as the source of the infection. This possible source was considered the more likely on account of the pool being more turbid than usual due to a preceding rain that had washed the surrounding

drainage area, mostly orchard lands. However, of the thirty odd persons who were in swimming, only ten became ill. On the other hand, one adult (case C C) who became infected was known not to have been in or close to the pool. The boys changed clothes at various places behind a thicket of small trees and bushes. It was not possible to correlate the cases with any particular place in the brush. No one encountered a living or dead rodent in or near the pool. Insect bites were experienced by many who visited the pool, and by all who took ill, but only one patient (case C C) was able to identify at least one species of insect, these she identified as hymenoptera of the genus, *Halictus*, popularly known as "sweat bees". The latter fact was corroborated by another adult who was stung by sweat bees and possibly had a mild attack of the disease, but whose case was not investigated serologically, and was not included in this series. Whether fleas also were present or absent was not determined, but they were known to be a common pest elsewhere about the countryside at that time. With a high degree of probability it was possible to exclude ticks, blood-sucking bugs (hemiptera) and mites (chiggers) as the actual vector.

That the disease was not caused by a typhoid or paratyphoid organism was evident from the negative findings (by agglutination and culture) made on blood and stool specimens sent from several of the cases to the Illinois State Board of Health Laboratory, Springfield, Illinois.

CASE HISTORIES

Case I H U (Case of Dr. Frank N. Wells). A tall, spare built lad of 14 years

of age. He had been quite well for the preceding several years. Without prodromes, he became suddenly ill on the evening of Friday, August 5, the onset being characterized by headache, lassitude, malaise, broken slumber, and coldness such as led him to keep under heavy bed covers on a hot day, but chill and rigors were absent. His temperature at noon the next day was 102.5°F , rising steadily to 105°F by that evening. Thereafter, for forty-eight hours the fever continued constantly at 104° to 104.4°F , except for brief periods following spontaneous hyperhidrosis, when it fell to 102.5° or 103°F . Drenching sweats, occurring every three or four hours, were a feature of this case from shortly after onset until after defervescence. Sleep occurred only for brief periods following the sweats, and was troubled with frightful dreams. Between naps there was no drowsiness or delirium, the sensorium being clear but without ability to concentrate.

By the end of the first 24 hours the face was flushed and the eyes became "terribly blood shot"—shot with red—and sore in their sockets, but the eyes did not run, there was no sore throat at any time. Headache persisted from onset, but nausea did not develop at once, the patient vomiting for the first time about 48 hours after onset. Vomiting persisted for three days, possibly due partly to exhibition of calomel. The temperature was kept to 104°F the third (Monday) night by constant all-over cool sponging, the pulse then being 110 to 116, but cyanosis such as could be recognized by a layman was not present.

Three and one-half days after onset the boy broke out with a nonpruritic, macular, nonhemorrhagic rash of splotchy appearance and deep red color, that first appeared around his ankles and spread upwards throughout the day. His arms broke out Wednesday morning and the abdomen and face during the afternoon of the same day. Twelve hours later the rash faded quickly, with abatement of the fever, but returned later the evening with a return of the fever. The face also soon extended over the rest of the body. The eruption was not accompanied by any other symptoms.

moved the dejecta had an unbearable odor. Dysuria was never present.

Case II R N (Case of Dr Wells). A nine year old boy, previously healthy. He experienced no prodromes. The onset was sudden and violent Saturday morning, August 6. The onset was characterized by nausea and terrible headache, with rise of temperature to 102°F (at 8 A M), and a slight feeling of chilliness but no chill. Nausea and headache persisted throughout the day, a stiff neck, without local tenderness or cervical adenopathy supervening. The temperature rose to 103.6°F (6 P M) the face becoming flushed, and the conjunctivae intensely congested, but sneezing or rhinorrhea were at no time in evidence. That night the boy did not sleep, the fever rose to 104.5°F , he vomited the next morning. For two and one-half days the patient was "bordering on delirium", with a constant temperature of 105°F , reaching 106.4° (axillary) at 4 P M Wednesday, but falling by the early part of next day. Hyperhidrosis was not a pronounced feature. A right inguinal adenopathy was noticed during the early course of the disease. After the fifth day a dry hacking cough, "but nothing of pronounced degree" occurred for three days.

The pulse was slow, weak and intermittent throughout Friday and Saturday, the seventh and eighth days of the disease. A stubborn constipation, noticed shortly after onset, persisted throughout the disease. A secondary rise of temperature, to 102°F occurred on the seventh day. No rash had appeared at any time, but on the eleventh day it was observed that the previously noticed "bites" had become minute lard papules and totally anemic (intensely white) in color.

Case III R McR (Case of Dr McRaven). A 10 year old boy with a history of having had two or three prior attacks of abdominal distress, but none for the preceding eight months. He became suddenly ill Sunday evening, August 7, with chilliness (but no chill), tongue, and a rapid rise of temperature. He had no delirium or depression or vomiting at onset. His temperature varied between 105°F and 105.5°F for three days and then fell to 104°F on the fourth day.

normal While the fever was high his face was flushed, his conjunctivae were congested and his bowels were constipated, but he was without lacrymation, coryza, sore throat or bronchitis He had no rash, and his sensorium remained clear

Abdominal tenderness and vomiting supervened after the second day of fever, and again during the secondary rise of his fever, but as the latter attack appeared to be a recrudescence of his previous appendiceal trouble, he was hospitalized and no longer considered an uncomplicated medical case

Case IV L G (Case of Dr Peacock)
An 11 year old boy, not previously ill He had a prodromal malaise for some ten hours before onset Onset was Saturday evening, August 6, with headache, stomachache and rise of temperature to 102.5° F He did not vomit at onset or at any time afterwards, although his head ached almost constantly throughout the course of disease, and stomach ached from time to time After the first twelve hours the temperature rose to 104.5° F and continued thereabouts constantly for three days, reaching 105° F in the evening of the fourth day, and thence twelve hours later declined by a rapid lysis Shortly after onset his eyes became blood shot and his condition progressed to what was called a dry granulation of his lids, with photophobia but without a mucoid or purulent exudate His throat at no time became injected or sore although he had a slight cough towards the end of the fever His doctor thought he heard some fine râles in the upper part of chest Constipation was not a marked feature, diarrhea did not develop There was no lymphadenopathy Following the lysis there were two or three remittances of the fever, but accurate records were not kept No rash developed Insect bites, believed to be mosquito bites, had been noticed

Case V D L (Case of Dr McRaven)
An anemic boy of small stature for his age of 13 years Some two to three weeks prior to his illness, his father had a short, prostrating fever with violent rigors and nausea but no sore throat, coryza, bronchitis or exanthem His mother and sister were likewise ill shortly afterwards, but only moderately to slightly so

The boy became ill suddenly, Saturday night, August 6, with headache, prostration and a sudden rise of temperature to 103° F He did not vomit until the next morning "His eyes became terribly blood shot and his nose ran although his throat was clear and not sore at any time For three days and three nights his fever was 103° F and did not vary the least at any time He developed a pain behind his ears and aches down his legs His bowels scarcely moved at all and never got loose About the fourth day his nose began to run, his eyes watered, and he developed a dry cough, after which he spat up a lot for a day or two His headache, which had gone away, came back terribly with the return of the fever" This patient had an abrupt lysis on the fourth day with intermittence of one day, and a secondary rise on the sixth His sensorium remained clear, and no rash developed Ten or eleven days after onset, his mother found noticeable for the first time, white macules about 3.5 mm in diameter These were scattered at random over the upper part of his chest, shoulders and neck On at least one, and probably two occasions, a week or so after defervescence, and following moderate exertion, he had a sharp rise of temperature lasting several hours

Case VI W K (Case of Dr McRaven)
A robust boy 12 years of age, not previously ill Onset was abrupt Saturday night, August 6, with slight malaise and chilliness, but without rigor or headache He did not vomit until the next morning (temperature then 103.4° F) The temperature taken Monday morning, when he again vomited, was 102° F, it was 103° that afternoon, and 104.8° that evening He had considerable injection of the conjunctivae (second and third days only) but had no lacrymation, coryza or sore throat This patient had no headache or pains at any time, and no cough at any time He was constipated throughout the whole course of the disease There was a lysis to subnormal (98.2°) about the middle of the fifth day, and thence a slight rise (to 99.6°) twelve hours later, the temperature remaining normal after the sixth day

Case VII L N (Case of Dr Wells) A boy thirteen years of age who had not previously been ill, was taken ill suddenly

on Sunday morning, August 7, the onset being characterized by dizziness, headache, nausea, and a rise of temperature to 102°F . He vomited shortly after onset and retched frequently and severely until the end of the third day, his temperature during the time rising to 104.4°F at 12 hours after onset, and thereafter remaining practically constant until the end of the fourth day. After a rapid lysis, and an intermission of one day (at 99.6°F), there was a rise to 103°F by the end of the following day, the temperature declining to subnormal (97°F) at the end of seventh day, but after the eighth day remaining nearly normal.

Towards the end of the fever this patient noticed some stiffness of his lower limbs. A nonproductive conjunctivitis was present, and the tongue was heavily coated, but there was no coryza, sorethroat, or cough. Constipation was troublesome throughout the whole course of the disease. The pulse (mostly 136 to 142) was unusually rapid for the temperature according to his mother, a trained nurse. Continuous drowsiness was a feature of this case.

On the ninth or tenth day after onset, the temperature then being normal, numerous anemic macules (white spots) were noticed for the first time on the upper part of his trunk. They were where small erythematous papules, 'insect bites', had been.

Case VIII E. A. (Case of Dr. McRaven). An active lad, $12\frac{1}{2}$ years of age, not previously ill. He became ill sometime Monday, August 8, there having been for some hours what might have been a prodromal period. The latter was characterized by an extreme sense of fatigue and weariness. Onset was with headache, flushed face, conjunctival engorgement, increased malaise, and a rise of temperature to 103°F . Chilliness and vomiting did not occur and nausea was at no time in evidence. Herpes labialis was noticed on the third day, but never was his throat sore. He never coughed, nor had any coryza or coryza. The fever reached 104.1°F at 36 hours after onset, and continued until, declining to 102°F on the following day, the next day, reaching to 101°F and then down, to 99°F on the eighth day. The temperature remained normal until the eleventh day, when it rose to 100°F and then down to 99°F on the thirteenth day, when it remained normal.

fifth and sixth days. There was a secondary rise (to 100.2°F) throughout the seventh day. Constipation occurred, with diarrhea at no time. The patient's sensorium remained clear. No rash developed. There was no remembrance of bone, joint or muscle pains, except for general "tiredness".

Case IX J. C. (Case of Dr. McRaven). A somewhat nervous lad of 11 years of age, not previously ill. He became ill rather suddenly on Monday evening, August 8. Onset was characterized chiefly by vertigo, sleeplessness and rise of temperature to 101°F , there being but slight chilliness. The next morning his "face and eyes looked real red and feverish, but his eyes did not water". During the day his temperature rose constantly, reaching 104.2°F , about 24 hours after onset. Twinges of sharp pain were noticed about that time and afterwards. He did not vomit at onset or during the first few days. He was constipated, the forced dejecta being dark green and black, and very offensive, a coated tongue was noted.

His temperature continued about constant at 103.6°F , during the second, third and fourth days, the general sweat, 48 hours after onset, and several slighter ones somewhat reducing it transitorily. There was no sore throat, coryza or chest symptoms at any time. A drop of his temperature to normal through the fifth day was followed by a rise to 100°F throughout the sixth day, exacerbation being accompanied by headache and vomiting. No rash appeared.

Case X was in a boy who visited the swimming pool about twenty-four hours after the day most of the boys were infected, and who at no time had been in contact with any one else who contracted the disease, or had partaken of food in common with them. The disease in this case was reported to have consisted of high continued fever with marked prostration, vomiting, and absence of respiratory tract symptoms and intestinal looseness. Although the disease was of the more severe sort, no rash developed. The incubation period was eleven days. Further information was not obtainable.

Case XI Mrs. C. C. This patient is a woman, 48 years of age, who had had a fever for several days, and a high abdominal pain.

was done two years previously. She was not robust but had been free from abdominal discomfort and febrile reaction during the preceding twelve months. She was seized Tuesday morning, Aug 9, with sudden profound weakness, chilliness, and general malaise, but without headache, rigor or definite nausea. Bites by insects (to a considerable extent) were sustained July 26. No conjunctivitis, coryza, sore throat, or chest symptoms developed at any time. Constipation was natural to her and was not replaced by any looseness. Diffuse abdominal soreness, without nausea, but with pains in the sides and the back, was a prominent feature of this case. Frequent heavy sweats at irregular intervals and profound drowsiness, both of which lasted five or six days, were outstanding features. A temperature record was not preserved, but it was clear that after an illness of eight days she quite suddenly improved, and for the following weeks remained free from symptoms suggesting a focal infection. Although a definite retrospective diagnosis was not possible in this case, the apparent occurrence of an incubation period, the sudden onset of a se-

verely prostrating illness with numerous irregular sweats, the absence of symptoms suggesting one of the commoner focal ailments, and the sudden convalescence after eight days suggested that she may have had the benign typhus-like disease (a fact later confirmed serologically).

BLOOD MORPHOLOGY

No blood counts were made by the attending physicians during the early course and fastigium of the disease. While the blood picture as found by the author at the end of lysis, and recorded below, is not conclusive evidence of a particular type of reaction, nevertheless it is evident that the disease produced a secondary anemia of moderate degree, and a slight leucocytosis, the latter being due chiefly to an absolute and relative increase in the lymphocytes and mononuclears, a change almost invariably noted in the rickettsial group of diseases.

TABLE I
BLOOD COUNTS TOWARD END OF THE DISEASE

CASE	AGE OF PATIENT	DAY OF DISEASE	W B C COUNT	R B C COUNT	HEMO- GLOBIN	INDEX CORRECTED FOR AGE NORMS	OTHER FORMED ELEMENTS
I H U	14	95	8,100	5,200,000	55%	0.70	Platelets +
II R N	9	9	8,550		60%		Platelets ++
V D L	13	9	9,000	5,100,000	55%	0.70	Platelets ++
VI W K	12	8	10,000	5,250,000	70%	0.90	Normal
VII L N	13	8	8,700	5,320,000	65%	0.80	Platelets ++
VIII E A	12.5	8	9,100	5,200,000	60%	0.75	Dust increased
Average	12.3	8.6	8,900	5,214,000	61%	0.77	Platelets +

TABLE II
DIFFERENTIAL COUNTS

CASE	AGE OF PATIENT	DAY OF DISEASE	BAS	EOS	MY	J	ST	SEGS	LYMPHS	MONOS	TRANS
I H U	14	95	0.0	14	0	0	10	43.1	47.7	6	0.9
II R N	9	9	0.7	7.0	0	0	0.7	45	40	5	
V D L	13	9	0.0	2.2	0	0	14	37	50	9	0.4
VI W K	12	8	0.0	2.4	0	0	16	51	40	5	0.0
VII L N	13	8	0.5	2.5	0	0	15	45	38	12	0.5
VIII E A	12.5	8	0.4	2.6	0	0	10	37	47	12	
Average	12.3	8.6	0.3	3.0	0	0	12	43	43.8	8	

SEROLOGY

Specimens of six sera were titrated against two local strains of *Proteus* of unknown type, but for the purpose of this article known as M₁ and M₂. While our titrations against these strains gave fairly significant results it was thought best to ask that titrations be made against a large number of strains of *Proteus* X organisms. Accordingly, six samples of the sera were sent to the National Institute of Health, Washington, D C, and six samples to the Rocky Mountain Spot-

"These serums have been run against *B proteus* X₁₀—No 504, which our experience has shown to be the most sensitive of our stock cultures of *B proteus*. The result as shown on the enclosed sheet are suggestive that the cases are either typhus or mild spotted fever, and we would suggest since these samples were taken about the 8th or 9th day of fever, second samples be withdrawn sometime after the end of the second week. They may show a much higher titer."

Titration at the National Institute of Health were made against only *B proteus* OX₁₀—No 504. The protocol of these titrations is as follows

TABL III
TITRATIONS AGAINST PROTEUS OX₁₀—No 504

CASE			DAYS AFTER ONSET	N H I NO	1/20	1/40	1/80	1/160	1/320	1/640
I	H	U	9 5	3248	4	4	2	0	0	0
II	R	N	9	3247	4	4	2	0	0	0
V.	D	L	9	3249	4	4	4	4	2	0
VI	W	K	8	3251	4	4	0	0	0	0
VII.	L	N	8		4	4	4	4	2	0
VIII	F	A	8	3250	4	4	4	4	0	0

ted Fever Laboratory, Hamilton, Montana. In each instance it was asked that the sera be titrated against the following strains of *Proteus* X ONK, HNK OX₂, OX₁₀, HX₁₀, W (N H I No 533), 271, 560, and 568.

To determine whether there was an increase in the titer during convalescence, the following specimens of blood drawn 18 to 20 5 days after onset (or about 9 to 10 days after defervescence) were titrated against strain No 504 with the following results:

In reply to our request, Dr R E

CASE			DAYS AFTER ONSET	1/20	1/40	1/80	1/160	1/320	1/640
II	R.	N	20 5	4	4	4	2	2	0
V	D	I	20	4	4	0	0	0	0
VII	L	N	19 5	0	0	0	0	0	0
VIII	F	A	19	4	4	4	0	0	0
IX	J.	C*	18 5	0	0	0	0	0	0
XI	C.	C*	18	4	4	2	0	0	0

*No fever reported at the time

Dr. Acting Director of the National Institute of Health, under date of August 22, 1922, as follows:

The protocol of the titration made at the Rocky Mountain Spotted Fever Laboratory is as follows:

TABLE IV
AGGLUTINATION TITERS FOR PROTEUS X STRAINS—LIVE ANTIGENS

CASE	AGE OF DAYS	PATIENT	AFTER ONSET	OX ₁₀ —No 504				OX ₁₀ No 271		OX ₁₀ No 560		OX ₁₀ —No 1		
				1/20	1/40	1/80	1/160	1/20	1/40	1/20	1/40	1/20	1/40	1/80
I	H	U	14	95	4	2	0	0				2	0	0
II	R	N	9	9	0	0	0	0				0	0	0
V	D	L	13	9	4	4	4	2				4	4	2
VI	W	K	12	8	4	4	2	0	4	2	4	2		
VII	L	N	13	8	2	0	0	0				0	0	0

KINGSBURY STRAINS

			OXK				HXX			HW		OX ₁₀ —No 2			
			1/10	1/20	1/40	1/80	1/20	1/40	1/80	1/20	1/40	1/20	1/40	1/80	1/160
I	H	U					4	2	0	2	0	2	0	0	0
V	D	L		4	4	2	4	4	2			4	4	4	2
	D	L*		2	0	0	2	0	0						
VI	W	K					4	2	0	4	0				
VII	L	N		4	2	0						2	0	0	0
VIII	E	A*	2	0	0	0									

*National Institute of Health

Eight to nine days after onset, none of the cases agglutinated the X₂ strains. However, blood drawn eleven days later, from cases II, V, VII, VIII, and XI, showed a very low and incomplete titer for both HX₂ and OX₂.

Comments of Dr R R Parker, Special Expert in charge of the Rocky Mountain Spotted Fever Laboratory, under date of August 26, 1932, were as follows:

"As a result of our experience with this agglutination test in Rocky Mountain spotted fever, I would be inclined to feel that these results mean little, either in a negative or positive way. Identical results with those listed could be secured with perfectly good clinical cases of Rocky Mountain spotted fever. We could also secure as high agglutinin titer as the highest shown in your series with the sera of occasional persons whom there is no reason to suspect have ever had a typhus-like infection. I offer these comments for whatever you may think them worth.

"The result of possible significance in connection with these tests is that the sera

of Underwood, Kern, Logsdon, and Niebur all show some agglutination of the Kingsbury strains, either OXK, HXX, or both. The agglutinin titer is, of course, very low, but in our experience it is very seldom that either a normal or a spotted fever serum causes agglutination of this strain even at 1:10. As possibly you may know from the literature, there are certain of the typhus-like infections that agglutinate Kingsbury strains more consistently than any other *Proteus X* organism.

"Certainly one has to admit that the possibilities of transmission of typhus-like diseases by biting insects have only been touched."

Concerning an increase in titer of sera drawn from four cases (cases II, V, VII, VIII) on the eighteenth to nineteenth day after onset, Dr Parker, under date of Sept 22 1932, wrote as follows:

"I am forwarding the results of the agglutination tests with the second group of six sera. It appears difficult to draw any definite conclusions from these results. Possibly the most suggestive data are those for the Richard Niebur case, in which all three

protus strains used for the first test and found negative showed low agglutination for the sample of Sept 7. The two samples for Logsdon show no essential difference. The second sample for Louis Niebur shows a slightly increased titer against two strains. These are the same two strains that showed increased titer in the second sample from Richard Niebur. This may be of some significance."

ANIMAL INOCULATIONS

Seven healthy guinea pigs weighing from 236 to 810 grams were inoculated, each with one blood specimen from one of the cases indicated in the accompanying protocol. The blood was injected intraperitoneally after the abdomen had been shaved and wiped with merthiolate 1-1000. In several instances a minute amount of the blood specimen was injected into the cornea of one eye.

Concerning what may be regarded as a febrile reaction in guinea pigs it has been our experience that a normal *average* temperature for pigs of the ages used in our experiments, and kept under optimum housing and nutritional conditions at a room temperature of 80° F (26.7° C), may be determined as being approximately 102.4° F (39.1° C) with maximum *average* variations from 101.5° F (38.6° C) before morning feeding, to 102.6° F (39.2° C)

after afternoon feeding, younger pigs usually having a slightly higher temperature than older pigs. In individual cases the range of normal is from 100.8° F (38.2° C) to 103.6° F (39.8° C). Hence in testing out individual pigs a temperature up to 103.6° F should be considered within the range of normal. When, however, the temperatures of a number of guinea pigs submitted to a group experiment are taken at the same time and averaged together for the purpose of constructing a histogram of the average temperature, it seems proper to compare the ascertained average with the known normal average under the prevailing housing and nutritional conditions. It is on that basis, therefore, that the following graph (see chart II) has been prepared. For the daily temperature readings of the individual guinea pigs see table IX.

Towards determining whether the virus causative of these cases was that of typhus fever or spotted fever, or possibly a yet unidentified typhus-like virus, it became necessary to determine whether the disease produced in the guinea pigs by the unknown virus left them susceptible to or wholly or partially immune to test viruses of known character: those of spotted fever and of typhus fever. Accordingly, blood virus of known character was inoculated as indicated in table VII. This table is a consolidation of observation

TABLE V
RESULTS OF GUINEA PIG INOCULATIONS

CASE			NUMBER (WEIGHT OF)	AMOUNT OF BLOOD CUP EXTRACTED	AMOUNT INJECTED	APPROXIMATE AMOUNT PER PUB	DAYS AFTER ONSET OF DISEASE	RESULTS*	PA
								MAX TEMP	
I	H	L	570 (gm)	0.4 cc	0.71 cc	0.71 cc	9.5	Positive (104.9°)	7th
II	P	N	~10	0.7 cc	0.86 cc	0.86 cc	9	Positive (105.4°)	7th
V	D	I	~55	1.3 cc	2.00 cc	2.00 cc	9	Positive (105.1°)	7th
VI	W	F	70°	1.8 cc	2.50 cc	2.50 cc	8	Positive (105.0°)	7th
* Positive = 100% (100%); Negative = 0% (0%); Doubtful = 50% (50%)									
II	P	N	236	0.6 cc	0.60 cc	0.60 cc	9	Negative	
VII	L	N	241	1.15 cc	4.75 cc	4.75 cc	8	Negative	
VIII	L	A	251	1.0 cc	1.00 cc	1.00 cc	8	Positive (107.6°)	5th

* Positive = 100% (100%); Negative = 0% (0%); Doubtful = 50% (50%)

made independently by the author, and by Dr R R Parker at the Rocky Mountain Spotted Fever Laboratory. Dr Parker kindly furnished us with Rocky Mountain spotted fever blood virus to make our tests, but as there was the possibility of the spotted fever losing potency in transit, we shipped four of our guinea pigs to Dr Parker, who kindly carried out cross-inoculation tests on them. Similarly, five of our pigs infected with the unknown virus, after we tested them against spotted fever virus, were shipped to Dr R E Dyer, Acting Director, National Institute of Health, Washington, D C, where they were cross-inoculated with typhus. The protocols of the cross-immunity tests are set forth in tables VII and VIII.

To determine whether persons con-

valescent from the benign rickettsial fever still carried the live virus in their blood, six guinea pigs were inoculated, each with the fresh whole, non-citrated blood of one case drawn on the eighteenth to twentieth day after onset. The results are set forth in table IX.

COMPARATIVE PATHOLOGY

Numerous typhus,^{2,17,22} typhus-like,^{4,15,23,28} and spotted fevers,^{12,19,20,26} of diverse types have been described in recent years. Lately these fevers have been arranged systematically according to their serologic reactions, their clinical manifestations, and the biologic positions of the vectors involved in their transmission.³¹ On that account it is now inadequate to give a clinical description of a typhus-like disease without accompanying the report with

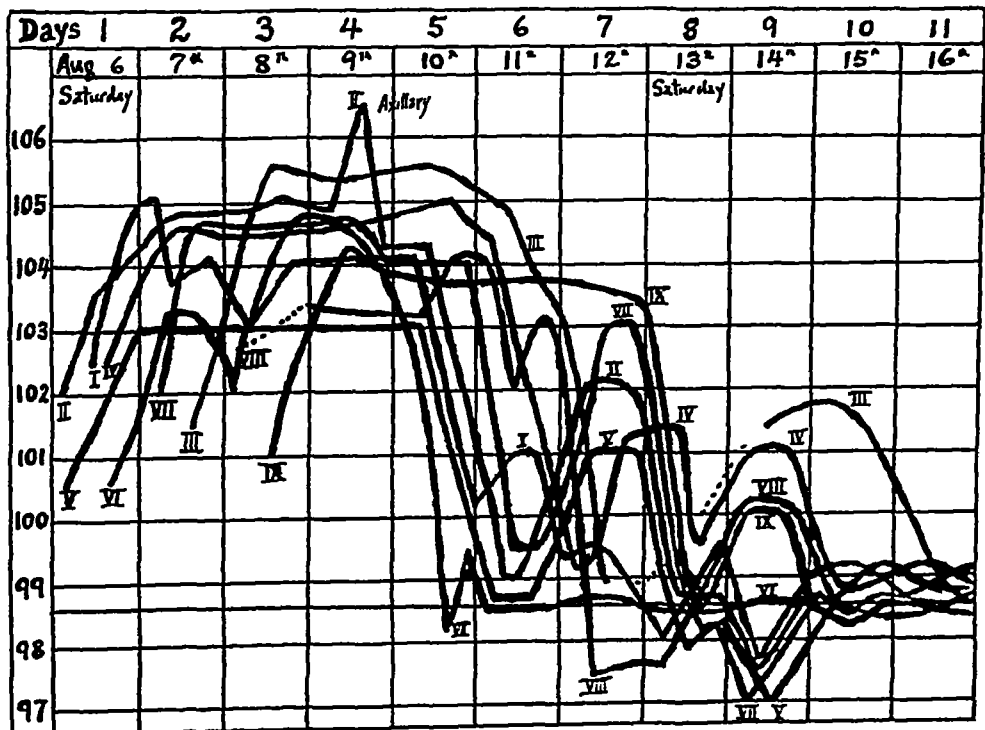


CHART I
TEMPERATURE CURVES OF NINE CASES

TABLE VI
DEMONSTRATIONS OF RICKETTSIAL ORGANISMS

	CASF	GUINEA PIG NO	SEX	SMEAR FROM TESTICLE	PERITONEAL SCRAPING	CORNEAL PUNCTURE	SECTION OF BRAIN
I	H. U	570	F	Not made	Not made	Grossly negative	Not made
II	R N	810	M	Not made	Not made	Grossly negative	Not made
II	R N	595	M	Positive	Positive	Not made	Positive
V	D L	885	F	Not made	Not made	Grossly negative	Not made
VI	W K	705	F	Not made	Positive	Microscop positive	Positive
VII.	L N	666	M	Positive	Not made	Not made	Not made
XI	C C	732	M	Positive	Positive	Not made	Positive

Guinea pig numbers indicate weight in grams of respective animals when first taken for experimental purposes. All guinea pigs lost from 24 per cent to 30 per cent (average 26 per cent) of their weight as a result of the typhus-like infection.

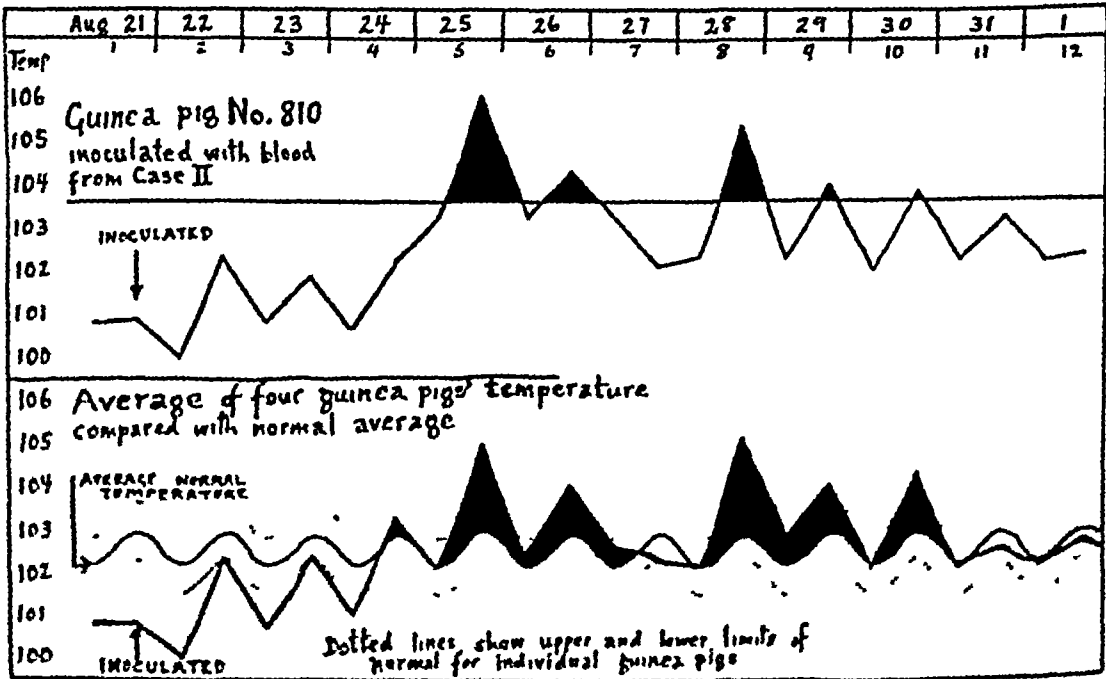


CHART II

TEMPERATURE CURVES OF THE DISEASE IN GUINEA PIGS

The upper curve represents typical temperature curve of individual guinea pig charted by the U. S. Public Health Service (recognizing as typhus-like infection).

The lower curve represents the average temperature of four guinea pigs (Case II, III, IV, V) which were inoculated with a blood smear from one of four cases (Case II).

The dotted lines show the upper and lower limits of normal for individual guinea pigs.

TABLE VII
CROSS-IMMUNITY TESTS AGAINST ROCKY MOUNTAIN SPOTTED FEVER

CASE	GUINEA PIG NO	TEST MADE BY	AMT R.M S F VIRUS INOCULATED	ORIGINAL INOCULATION	RESULTS	FOR TEMP CURVE SEE TABLE X
I H U	570	Parker		9 5 day blood kept 6 days	Susceptible to R M S F *	
II R N	810	Toomey	15 cc	9th day blood kept 6 days	Delayed, mild reaction to R M S F	Item 14
II R N	236	Toomey	10 cc	9th day blood kept 8 days	Almost immune to R M S F	Item 15
V D L	885	Toomey	10 cc	9th day blood kept 6 days	Immune to R M S F	Item 16
V D L	503	Parker		Convalescent's 20th day, direct	Susceptible to R M S F *	
VII L N	240	Toomey	10 cc	8th day blood kept 8 days	Delayed, mild reaction to R M S F	Item 17
VII L N	666	Toomey	10 cc	Convalescent's 19 5 day, direct	Excluded account wasting disease	Item 18
VIII E A	750	Parker		8th day blood kept 8 days	Susceptible to R M S F *	
IX J C	381	Parker		Convalescent's 18 5 day, direct	Susceptible to R M S F *	
Controls	564	Toomey	10 cc		Positive, mild	See Item 19
	407	Toomey	10 cc		Positive, typical	Item 20
	770	Toomey	15 cc		Positive, very mild	Item 21

* Letter report by Dr R R Parker, October 4, 1932

TABLE VIII
CROSS IMMUNITY TESTS AGAINST TYPHUS FEVER

CASE	GUINEA PIG NO	TEST MADE BY	ORIGINAL INOCULATION	RESULTS
II R N	810	Dyer	9th day blood	All survivors were sus- ceptible to endemic ty- phus *
II R N	236	Dyer	9th day blood	
V D L	885	Dyer	9th day blood	
VII L N	240	Dyer	9th day blood	
VIII E A	610	Dyer	Convalescent's	

* Letter report by Dr G W McCoy, Director, National Institute of Health, October 8., 1932, as follows 'The five guinea pigs received from you on September 22 have been tested for immunity to endemic typhus as you requested Three of them gave the usual reaction of fever and redness and swelling of the scrotum and hence were considered non-immune to endemic typhus, while two of them died during the course of the test, presumably from secondary infection, and it could not be determined whether they were immune'

TABLE IX
TESTS FOR VIRULENCY OF CONVALESCENTS' WHOLE BLOOD

CASE	GUINEA PIG NO	SEX	DAYS AFTER ONSET	AMT OF BLOOD INJECTED	CC PER KILO	RESULTS*
II R N	595	M	20 5	4 5	7 5	Very virulent
V D L	503	M	20	9 1	20 0	Virulent
						Probable but
VII L N	666	M	19 5	5 0	7 5	uncertain
VIII E A	610	M	19	5 0	8 2	Very mild
IX J C	381	M	18 5	4 7	12 4	Virulent
XI C C	732	M	18 5	5 5	7 5	Virulent

*For daily temperature readings of these guinea pigs see table X

TABLE X
TEMPERATURE READINGS OF GUINEA PIGS*

Inoculations with Unknown Virus in Blood Drawn 8th to 9th Day of Disease													
ITEM	PIG NO	DATE	AUG 21	22	23	24	25	26	27	28	29	30	31 1
			x										
1	570	*8,8	1,22	10,22	14,30	22,48	27,38	28,25	26,49	33,42	29,39	21,27	22,22
2	810	8,9	0,24	9,18	6,26	31,60	31,43	32,22	24,54	23,40	20,38	22,32	23,24
3	885	8,8	0,24	8,25	12,37	19,44	14,37	23,21	18,51	30,42	21,39	20,20	19,24
4	705	8,8	0,26	0,21	10,34	21,50	24,42	26,23	24,50	26,36	13,37	21,23	20,26
Average		8,8	0,24	7,24	10,32	23,50	24,40	27,23	23,51	28,40	21,38	21,25	21,24
			x										
5	236			13,0	0,11	2,4	10,16	8,8	12,24	13,25	6,23	8,22	8,
6	240			14,26	0,11	5,4	14,18	10,0	10,30	14,30	17,29	14,28	13,
7	750			10,12	0,12	34,61	34,52	30,30	10,56	29,43	34,48	34,38	32,37

Tests for Virulency of Convalescent's Whole Blood

	Aug	26	27	28	29	30	31	1	2	3
8	595	19	26,40	42,62	48,	Dead				
9	503	25	20,23	41,51	40,36	17,40	24,41	26,43	21,41	To Dr R R Parker
10	666	19	26,34	22,45	38,38	17,42	23,44	20,23	10,10	Required for R M S. fever cross-inoculat
		x								
11	610	21	12,18	40,48	32,36	11,39	21,40	22,42	20,39	
12	381	26	22,26	24,54	22,42	14,40	20,41	22,42	21,40	To Dr R R Parker
13	732	22	26,22	31,52	36,40	20,22	19,17	14,15	10,	Dead

Immunes to Unknown Virus Cross Inoculated with R M S F Virus

	SEPT	2	3	4	5	6	7	8	9	10	11
14	810	27,29	15,24	20,40	11,24	20,21	22,28	21,25	21,40	37,28	22,
15	236	33,36	24,24	19,38	38,32	38,40	34,33	31,30	32,38	32,38	30,
16	885	19,10	16,20	10,34	20,22	20,22	20,22	22,27	27,30	27,24	24,
17	240	32,22	29,24	18,33	33,34	33,31	24,26	31,33	30,50	38,38	36,
18	666	10,10	11,13	3,2	0,11	2,5	2,5	4,8	5,11	6,10	7,
19	564	17,20	16,20	7,21	18,44	8,39	10,40	11,40	22,38	38,26	28,
20	407	16,20	14,26	13,7	26,21	20,40	20,37	42,60	61,62	60,59	40,36
21	770	16,34	15,22	13,39	30,24	12,30	11,31	19,36	37,39	38,26	32,37

*Pairs of numbers represent morning temperature (on left) and evening temperature (on right) of same day, days are in chronological order from left to right. Numbers are tenths degrees above 100°, example, 35 = 103.5° F., 0 = any temperature 100° F. or under
x = time inoculated

pertinent serologic and immunologic data

As to what criteria will prove to be the ultimate means for classifying the fevers of the typhus-spotted fever group can not be predicted with assurance, but those tests that establish the normal relationships of these fevers will naturally be accepted as the best. Since then any of these criteria, serologic, immunologic, the power to agglutinate, or the agglutinating

properties of the blood with respect to the different strains of the Proteus X¹⁹¹⁴⁻¹⁶⁻²¹. Whether the diverse agglutination characteristics of these diseases can be dependably correlated with their immunological differences can not at present be accepted with finality, although it does appear that the power to agglutinate either or both of the X., or the Kingbury strain is a differentiating criterion of fundamental value.

While the behavior of these viruses when inoculated into guinea pigs has been studied by several observers,^{1,5,6,7,8,11,20} it appears that the febrile, peritoneal, scrotal, and perhaps cerebral reactions are conditioned as much or more by the degree (state) of virulency of the virus employed, than by its individual character. Thus scrotal lesions are common in the malignant form of Rocky Mountain spotted fever but may be absent in the mild forms of the disease. They are not common in the epidemic typhus of Europe but are common in certain of the American and Mexican strains of typhus fever,^{1,6,30} although occasionally absent in those infections, and occasionally observed in the epidemic typhus of Europe.^{7,30}

In comparison with the other diseases of the typhus-spotted fever group, the disease described in this report has a unique place. We remark it having a rash somewhat similar to the spotted fever of the Rocky Mountains, at least with respect to its upward progression from the ankles. Also, the disease appeared to give a partial, but apparently incomplete immunity to spotted fever. On the other hand it caused agglutination of the Kingsbury strains of *Proteus* HK and OK, something that Rocky Mountain spotted fever seldom does. Also there was a longer incubation period in the guinea pig and not as great a degree of scrotal reaction as one might expect in spotted fever, although in the eastern-southeastern states' strain of spotted fever, the scrotal reaction is not commonly observed. Ticks, the so-far-as-known only vectors of Rocky Mountain spotted fever could be ex-

cluded as the vectors of this disease. This fact raises the question whether the virus concerned was that of spotted fever somewhat altered by being adapted to a vector of a different biologic order.

In comparison with the diseases known to agglutinate the Kingsbury strains, the scrub typhus of Malasia, pseudotyphus of Sumatra, tsutsugamushi disease, and tick-bite fever of South Africa, we note them as usually having a primary sore, as invariably (?) having a rash, a more prolonged febrile course, and more pronounced nervous symptoms. In fact our benign sporadic disease is clinically less similar to the Kingsbury group of diseases than to endemic typhus, especially a mild endemic typhus *sine exanthem*. As to one other fever in which the Weil-Felix test has been found positive, the Port Elizabeth fever,²⁴ we note the latter's prevalently low, irregular fever, the nervous symptoms and the rash, a syndrome quite distinct from that found in our disease.

When compared with the tick-borne *fièvre boutonneuse* (exanthematic fever) and the tick typhus of India, diseases somewhat resembling Rocky Mountain spotted fever, we find no resemblance to them greater than our disease has to spotted fever of the Rocky Mountains. On the other hand, of the tick-borne group we find the greatest similarity between our present disease and the (non-exanthematic) American mountain tick-fever described by us as a distinct entity about a year ago.^{21,25} So close is this resemblance that it would at times be impossible to distinguish between these

diseases by clinical means alone, the main differences at most being that the American mountain tick-fever has a shorter incubation period, is usually accompanied by more aches and pains of muscles and bones and runs a slightly longer course with two or three remissions instead of one, but these clinical differences could be due to our present disease being caused by a less virulent strain of the same virus.

As to our present disease being a mild typhus *sine exanthem*, we can say that the low *Proteus* X_{10} titer, the mononuclear rather than a lymphocytic leucocytosis, the absence of scrotal lesions in guinea pigs, and the less accentuated disturbance of the nervous, circulatory and bronchial systems are against such a supposition.

SUMMARY AND CONCLUSIONS

An intensely febrile typhus-like disease of short duration was observed to cause a sharply localized group of cases in the west-central part of Illinois during early August, 1932. Of the eleven known cases, ten were without exanthem. One case developed on the fourth day a lenticular, ascending, non-hemorrhagic erythematous macular rash somewhat resembling the rash of mild Rocky Mountain spotted fever except that it disappeared suddenly with the lysis of the fever.

The disease was characterized by an incubation period of about twelve days, by sudden onset, abrupt rise of temperature usually with headache, chills, prostration, and by a high continued fever that fell abruptly 3 to 5 days after the onset. A remission occurred in 10 of 11 cases, frequently followed by a second rise of temperature.

requently followed by a secondary rise of temperature lasting one day. Constipation and an intense non-productive conjunctivitis (not accompanied by lacrymation) were characteristic symptoms. Coryza, pharyngeal engorgement and chest symptoms were wholly absent, except for an occasional slight dry cough towards the end of the disease. Neuralgic and rheumatoid pains were almost wholly absent, and the sensorium remained clear. Hyperhidrosis and a regional lymphadenopathy were occasionally observed, but were not constant features of the disease. There was no mortality.

The disease caused a slight leucocytosis due to a relative and absolute increase in the lymphocytes and large mononuclears, particularly the latter. Considerable secondary anemia developed, but convalescence was rapid.

Although the disease was undoubtedly insect borne, a primary sore at site of inoculation could not be made out in any case. Small erythematous papules, the sites of insect bites, were commonly observed to become anemic (white macules) following the termination of the fever. The vector was not identified but there was evidence suggesting that the virus was transmitted by a hymenopteron of the genus *Halictus* (family Halictidae).

Agglutination tests against strains of *Proteus* X organisms showed an affinity for the non-indologenic or Kingsbury strains in addition to a moderate affinity for the X_{10} strain. The X_2 strain were not significantly agglutinated. There was an increase and at most very slight increase in the agglutination titer during convalescence.

Guinea pigs were found moderately susceptible to the virus. The disease in guinea pigs was without a noticeable scrotal lesion and was principally neurotropic, thus resembling epidemic typhus more than certain strains of endemic typhus or Rocky Mountain spotted fever. Inoculation of convalescent guinea pigs with the virus of Rocky Mountain spotted fever showed that the guinea pigs were susceptible to the spotted fever virus but appeared to have a partial or group immunity to spotted fever.

Preliminary studies, not developed in this report, indicate that the disease occurs not uncommonly in a very mild form, and that it is the cause of some of the cases hitherto loosely called "summer flu" or influenza.

Clinically and immunologically it is necessary to recognize this disease as a separate entity. Serologically it is related to the diseases having an affinity

for the non-indologenic (Kingsbury) strains of the *Proteus X* organisms. An approximate clinical similarity to the American mountain tick-fever is noted.

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REFERENCES

- ¹ NEILL, M H. Experimental typhus, Pub Health Repts, 1917, *xx*, 1105.
- ² MACY, K F, and HAVENS, L C. A series of cases giving a positive Weil-Felix reaction, Am Jr Trop Med, 1923, *iii*, 495-507.
- ³ BREINL, F. Studies on the typhus virus in the louse, Jr Infect Dis, 1924, *xxiv*, 1-12.
- ⁴ FLETCHER, W, and LESSLAR, J E. Tropical typhus, Bull Inst Med Res, Federated Malay States, No 2, 1925, and Bull No 2, 1926.
- ⁵ BREINL, F. Effect of concurrence on typhus and Rocky Mountain spotted fever infections in guinea pigs, Jr Infect Dis, 1928, *xlii*, 48-55.
- ⁶ MOOSER, H. Reaction of guinea pigs to Mexican typhus (Tabardillo), Jr Am Med Assoc, 1928, *xc*, 19.
- ⁷ PINKERTON, H. Rickettsia-like organisms in scrotal sac of guinea pigs with European typhus, Jr Infect Dis, 1929, *xliv*, 337.
- ⁸ SPENCER, R R, and PARKER, R R. Studies on Rocky Mountain spotted fever. Variations in the behavior of the virus, Hygienic Lab Bull No 154, Washington, D C, Jan 1930, 49-60.
- ⁹ LEWTHWAITE, R. Experimental tropical typhus in laboratory animals, Bull Inst Med Res, Federated Malay States, No 3, 1930, 10 pp.
- ¹⁰ SPENCER, R R, and MACY, K F. The Weil-Felix reaction in endemic typhus fever and in Rocky Mountain spotted fever, Pub Health Rep, 1930, *vi*, 3-8.
- ¹¹ NAGAI, M, TAMURA, T, MITAMURA, T, and SATO, K. On the virus of tsutsugamushi disease and its demonstration by a new method, Japan Jr Exp Med, 1930, *viii*, 309-318.

- ¹² RUMFICH, A., DYER, R. E., and BADGER, L. F. The typhus-Rocky Mountain spotted fever group. An epidemiological and clinical study in the eastern and southeastern States, Pub Health Rpts, 1931, xlii, 470-480
- ¹³ BADGER, L. F., DYER, R. E., and RUMFICH, A. An infection of the Rocky Mountain spotted fever type. Identification in the eastern part of the United States, Pub Health Rpts, 1931, xlii, 463-470
- ¹⁴ FETIX, A., and RHODES, M. Serologic varieties of typhus fever, Jr Hyg, 1931, xxxi, 226-246
- ¹⁵ TROUP, J. McD., and PIPPER, A. Tick-bite fever in southern Africa, Lancet, 1931, ii, 1183-1186
- ¹⁶ PIPPER, A., and DAL, HELEN. An agglutination curve in tick-bite fever, Jr Med Assoc South Africa, 1931, v, 519-521
- ¹⁷ MONTEIRO, J. LIMOSS. Typho endemico de S. Paulo, Brasil-Medico, 1931, xlv, 1096-1100, 1109-1113, 1140-1142, 1163-1165, 1188-1190
- ¹⁸ MONTEIRO, J. L., DA FONSECA, F., and PRADO, A. Pesquisas sobre a possibilidade de transmissao experimental do virus por "Ixodidae", etc., Brasil-Medico, 1932, xlv, 49-52, 169-172, 193-195
- ¹⁹ KEMP, H. A., and GRIGSBY, C. M. The occurrence and identification of an infection of the Rocky Mountain spotted fever type in Texas, Texas State Jr Med, 1931, xxviii, 395-398
- ²⁰ TOOMEY, NOXON. Mountain fever and spotted fever of the Rocky Mountains—clinical studies. ANN INT MED, 1931, v, 545-600
- ²¹ TOOMEY, NOXON. American mountain tick fever and spotted fever of the Port Elizabeth type—comparative epidemiology, ANN INT MED, 1931, v, 601-612
- ²² CUSHING, H. B., and CALDWELL, R. J. Sporadic typhus fever, Canadian Med Assoc Jr, 1931, xxv, 649-653
- ²³ SCROGGIE, F. H. Fever with some resemblance to typhus fever occurring in Port Elizabeth and district, Jr Med Assoc South Africa, 1931, v, 809-814
- ²⁴ GRAY, F. C. A note on laboratory investigations of the Port Elizabeth type of fever, Jr Med Assoc South Africa, 1931, v, 814-816
- ²⁵ TOOMEY, NOXON. American mountain tick-fever semeiology and nosology. ANN INT MED, 1932, v, 912-923
- ²⁶ REIMANN, H. A., ULRICH, H. L., and FISHER, L. C. The differential diagnosis between typhus and spotted fever. Report of a case and the isolation of a new mild strain of spotted fever, Jr Am Med Assoc, 1932, xcvi, 1875-1879
- ²⁷ DAVIS, G. E., and PARKER, R. R. Observations on the agglutination of Proteus X organisms in Rocky Mountain spotted fever, Pub Health Rpts, 1932, xlvii, 1511-1521
- ²⁸ ROSS, G. R. Eruptive fevers of the typhus group, with notes on a fever of the group observed in Southern Rhodesia, South African Med. Jr, 1932, vi, 453-459
- ²⁹ DURAND, PAUL. La réaction de Weil-Felix dans la fièvre boutonneuse, Arch de l'Inst Pasteur de Tunis 1932, xv, 395-421
- ³⁰ DYER, R. E., BADGER, L. F., CROFT, E. F., and WORKMAN, W. G. Endemic typhus fever of the United States. History, epidemiology and mode of transmission, Jr Am Med Assoc, 1932, xcvi, 772-801

An Obstinate Case of Intestinal Myiasis

By W B HERMS, M A , *Berkeley, California*, and Q O GILBERT, M D ,
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BY the term *myiasis* is usually meant the invasion of organs or tissues of animals including man by the larvae of flies belonging to the order Diptera. Although there are a number of species of flies, notably the Oestridae (bots, warbles, etc.), in which this invasion is an obligatory form of parasitism there are many more species in which this is an accidental relationship, *i e*, the normal existence is free-living and invasion of the internal organs of higher animals is through ingestion of infested food or drink, or ingress through wounds or the natural openings (nasal and anal).

Among the more obviously free-living Diptera which have been definitely incriminated in intestinal myiasis is the cheese fly, *Piophilula casei*, which deposits its eggs in old cheeses, ham, bacon, and similar fatty products. It is easy to understand how larvae of this species might be ingested but it is not so easy to understand how the larvae could continue to live for any length of time in the intestine. Yet

Thebault¹ (1901) according to Riley and Johannsen² (1932) recovered living larvae of this species of fly from bloody excrement voided by a child. It has been shown experimentally that a dog fed on cheese containing these larvae suffered marked intestinal injury, the papillae of the small intestine having been destroyed in spots and the walls almost perforated, presumably the result of larval attack.

However, among the Diptera more commonly reported as causing intestinal myiasis are the lesser housefly, *Fannia canicularis* L., and the latrine fly, *Fannia scalaris*, F., neither of which breeds in materials which might normally be ingested in or with food, *i e*, their larval food is principally fecal material. Both species invade the house and, of course, might deposit eggs under stress of circumstances in decomposing vegetable matter or meat. Riley and Johannsen (*loc cit*) describe the symptoms caused by the invasion of these flies as vaguely resembling helminthiasis, or more specifically, "as causing vertigo, severe headache, nausea and vomiting, severe abdominal pains, and in some instances, bloody diarrhea." Living larvae have been recovered in stools.

Our concern in the case we are about to describe is with a group of flies which have a much wider range

From the Medical Entomology Laboratory of the Division of Entomology and Parasitology, University of California.

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observation she was given santonin by mouth and colonic irrigations containing thymol. Many larvae were recovered after this, all of which were dead. Following the attacks of diarrhea the patient had a number of severe hemorrhages. Tetrachlorethylene capsules were given by mouth but they caused gastric distress. In the hospital a duodenal tube was passed and tetrachlorethylene was injected beyond the stomach. For a few weeks there was apparent improvement, but the same attacks recurred, with the passage of larvae by vomiting and bowel discharge. In addition to the severe hemorrhages from the bowel, the patient vomited blood. There were bleeding hemorrhoids. It was necessary to give two blood transfusions in September, 1931, and again after another hemorrhage in November, 1931.

Once during the summer after tetrachlorethylene was given through a duodenal tube, 1,000 cc of a solution containing Epsom salts was administered at a temperature of 110°F. This gave no permanent result. At Christmas time, 1931, the patient found it necessary to go to the southern part of the state where her condition has remained unchanged.

THE LARVAE

Specimens of fly larvae as stated above were brought to the Medical Entomology Laboratory of the University of California on March 31, 1931. Two full grown larvae placed in a receptacle with dry sand, pupated, one during the following night, and the other April 1. The first winged fly emerged April 10, and the second, April 11. These were both blue bottle flies, *Calliphora* sp.

The second lot of larvae was received May 12. These were contained in very liquid feces and were less than half grown. Fifteen of these larvae were carefully transferred to a small piece of fresh fish in a jar with dry sand and the cover of the jar sealed with vaseline. The larvae grew rapidly and pupated May 22. Seven adult

flies emerged on June 4 and 5. These were green bottle flies, *Lucilia* sp. Three days later seven other flies emerged which belonged to still another genus, namely *Sarcophaga*, a species of larviparous grey flesh fly. The carefully sealed jar fully excluded any possibility of contamination on the part of flies from the outside, and the facts of the life history of these two species pointed positively to their origin as already explained.

On July 28, 1931, another lot of larvae was brought to our laboratories. These were in a specimen of stool, also very liquid. Three fully grown larvae were transferred to a jar with dry sand as before and on July 30 one pupated, the others died, and on August 11 an adult fly emerged which proved to be another blue bottle, *Calliphora* sp., like those of the first lot received, except that this specimen was decidedly undersized.

DISCUSSION

The food habits of the three genera of flies involved in this case of intestinal myiasis would seem to indicate that the original infection was due to the ingestion of cold meat, possibly pork in some form. The genus *Sarcophaga* is a strongly carnivorous group of flies which supports this theory, although the two other genera, *Lucilia* and *Calliphora*, are more omnivorous. The recurrence of violent symptoms with egestion of larvae in vomit and stools would ordinarily point to repeated infections like the original infection, but the fact remains that the patient lived in a way that would seem to preclude repeated infestations.

The other alternative explanation of the long period of maggot infestation and the periodic recurrence of violent symptoms is that of pedogenesis, *i.e.*, the production of other larvae on the part of fully grown larvae already in the digestive tract. Normal reproduction following the usual sequence of events, pupation, emergence of adult flies, fertilization, and egg laying (or viviparous larval production) all within the intestine of a human being, is extremely difficult to believe. Certainly there were broods of very young larvae at intervals, at which time also full grown larvae were present. No examination was made of these mature larvae for evidences of pedogenesis.

At least one instance of pedogenetic reproduction has been reported for *Calliphora*, that by Parker³ (1922), who states, "The increases led me to believe that *Calliphora erythrocephala* occasionally multiplies in an unusual way, and that this way is not polyembryony but pedogenesis"

In retrospect the patient must have had the condition of myiasis for a number of years because of the similarity of the many attacks. The condition complicated the protozoan infestation. There are at least three outstanding facts: (1) The condition was demonstrably present for at least a year, historically present for many years. (2) The attacks came at quite regular intervals, associated with great abdominal distress with the passage of feces by mouth and bowel. Following the attacks there would be a period of comparative quietness to be followed by the next attack with the abdominal distress. (3) During the past

year the patient lived in a clean modern home where the food was handled in a sanitary manner, and during the many times we were in the home no flies were seen. In view of these facts it seems impossible to explain the situation except on a basis of constant reproduction of the larvae within the gastro-intestinal tract, reaching a stage of maturity at intervals when the attacks would occur*.

Unfortunately the several species of flies involved in this case have a rather wide distribution, otherwise if one or more of these species were localized particularly in relation to Texas where the patient lived prior to coming to California, evidence would be at hand confirming our belief that this was a case of intestinal myiasis of long standing,—a very remarkable instance.

Our effort is now being directed toward a study of pedogenesis in the flesh flies. If we can produce artificial conditions simulating the digestive tract and can induce pedogenesis then, at least, a forward step has been made in the solution of our problem, but there would still remain to be had

*Note by the Editor. In response to inquiry as to the completeness with which extra-corporal contamination had been excluded, Dr. Gilbert replied as follows:

The specimens of feces sent to Dr. Herms were obtained either here at my home or while the patient was in Peralta Hospital. There was absolutely no chance of error in obtaining the specimens. They were obtained from defecation, from vomitus, from the rectum through a proctoscope. The specimens were kept and the specimens were retained more than a dozen hours before they were examined, usually in a cold place. The only article of clothing worn by the patient at the time of the attacks was a pair of

reason for the incomplete response to treatment, made difficult because of severe complications

Withal, the possibility of repeated

ingestion of larva- or egg-infested food, though hard to believe under the circumstances, is still not completely

ruled out

REFERENCES

¹THEBAULT, V Hemorrhagie intestinale et affection typhoïde causée par des larves de diptère, Arch Parasitol, 1901, iv, 353-361

²RILEY, W A, and JOHANNSEN, O A Medical entomology, insects and allied

forms which affect the health of man and animals, 1932, McGraw-Hill Book Company, Inc, New York, viii, 467

³PARKER, G H Possible pedogenesis in the blow-fly *Calliphora erythrocephala* Meigen, Psyche, 1922, xxix, 127-131

Familial Congenital Clubbing of Fingers and Toes

Report of a Case

By OSCAR B RAGINS, M D , and E B FREILICH, M D , *Chicago, Illinois*

CONGENITAL familial clubbing of fingers and toes is apparently a rare condition. A review of literature revealed no report of such conditions. We therefore thought the present example worthwhile reporting.

Mr. B , 34 years old, presented himself for examination with minor complaints of gastro-intestinal origin. Dur-

ing the course of examination, the peculiar clubbing of his fingers and toes was noted. There were no abnormal findings in his heart or lungs. Except for a slight tic of the palpebral muscles of his left eye, the physical examination was essentially negative.

The patient related that his sister, father, and paternal uncle have identical clubbing of their fingers and toes. He had no information as to the presence of this condition in any of his grandparents.

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X-ray study of various parts of his skeleton and cranium revealed that the distal phalanges of the upper and lower extremities show slight enlargement, but proportionate to the other bony structures. The middle phalanx of the toes is short and broad. There is thickening of the cortex and the periosteum of the radius, thickening and proliferation of the periosteum and cortex in several regions of the

tibiae and fibulae, and small exostoses in several regions of these bones.

It was noted by comparing the photographic picture and the x-ray of the hand that the clubbing of the fingers is much out of proportion to the deviation from the normal structure of the distal phalanges. Therefore the clubbing in this case affects mainly the soft tissues.

Complete Situs Transversus With Auricular Fibrillation and Flutter

Report of a Case

By HAROLD A. ROBINSON, M.D., *Detroit, Michigan*

THIS case is reported because of its interesting electro-cardiographic findings. A thorough search of the literature reveals no previous similar case reported. There are many cases reported in the literature of complete situs transversus with electrocardiographic depictions of dextrocardia. Some of them are associated with pathologic conditions of the heart, for the most part, congenital anomalies. Other case reports are of situs transversus associated with diseases other than those of the heart.

A discussion of complete situs transversus and auricular fibrillation and flutter will not be taken up here, having been thoroughly discussed in other reports in the literature.

In the absence of other congenital anomalies, there is no reason to expect an individual with complete situs transversus to differ from the normal individual in relation to health and disease. Post-mortem examinations, operative reports, study of patients with complete situs transversus afflicted with various diseases or in health, have demonstrated that the same morbid process can be found in that condition as in the normal individual. So that in complete situs transversus we may expect other

fibrillation and flutter, we would not expect that individual to differ from a normally developed individual with auricular fibrillation and flutter. And such is the case.

However, we would expect the electrocardiographic depictions to differ. In dextrocardia the electrocardiographic findings are inversion of P, QRS, and T waves in lead one. When associated with auricular fibrillation and flutter we would expect an inversion in lead one of the fibrillation and flutter, and such is the case. But an examination of the electrocardiogram without the history of dextrocardia would lead us to make another diagnosis as will be shown later.

CASE REPORT

S. B., a female, white and of Roumanian birth, 40 years of age, and married was first seen April 26, 1931. Her complaints were pain in heart, shortness of breath, and palpitation of heart.

Past history.—The patient denied having had rheumatic fever, chorea, influenza, scarlet fever, diphtheria, pneumonia and pleurisy. She had had occasional head colds and a sore throat in winter. An abdominal operation performed in 1914, for a hernia, was the only surgical experience. She denied any other medical experience.

Current history.—The patient was first seen at 33 years of age, the general symptoms of

every 28 days, of 3 to 5 days duration. Menses have been irregular since the onset of the present illness.

Family history Her father and mother are dead, of causes unknown to the patient. She knows nothing of constitutional diseases in the family.

Marital history Her husband is living and well. They have been married 14 years. One child died at the age of 4 months. The cause of death is unknown to the patient. There were no other pregnancies.

Occupation Housework.

Present illness The patient states that previous to January 1, 1931, she felt perfectly well. At that time she suffered a bad cold and had an abscessed tooth extracted. Since then she has noticed progressively increasing dyspnea, palpitation, and edema of the lower extremities, also associated weakness and dizziness when ambulatory. For two weeks before the time when she was first seen, she noticed a "flopping around" of the heart at times, and experienced occasional sharp pain over the normal cardiac area, to the left of the sternum radiating to the region of the left scapula.

Physical examination, April 26, 1931 The patient was seen lying in bed, obese, flushed, dyspneic in bed, not appearing acutely ill with mitral-type facies, not cyanotic and of cheerful disposition. Her eyes reacted to light and in accommodation. There was a slight injection of the pharynx, the tonsils were present but did not appear diseased.

Lungs Resonance was impaired and breath sounds absent in the lower right chest anteriorly. Normal resonance and breath sounds were found in the cardiac area. Posteriorly the lung fields were clear throughout. There were no râles.

Heart The left border of dulness was located one fingerbreadth to the left of the sternal margin. The right border of dulness was in the right axillary line. The apex impulse was felt in the right fifth intercostal space, almost out to the axillary line. The heart sounds were very distant in the usual cardiac area but were heard very distinctly, also, in their corresponding positions on the right side. The rhythm had a definite irregular irregularity. No definite murmurs were heard. A_2 was greater than P_2 . There was no increase in the retromanubrial dulness.

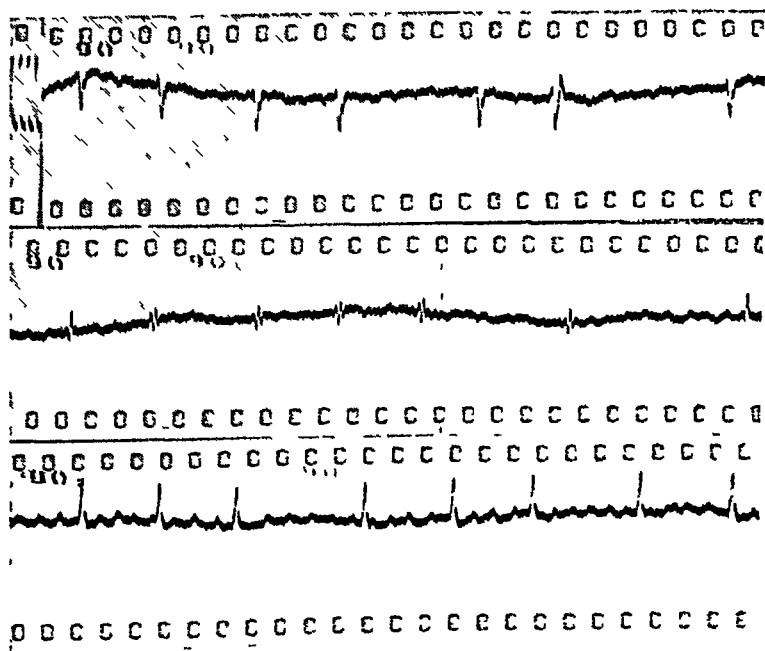


FIG 1 Electrocardiogram, April 26, 1931. Rate 110. Auricular fibrillation and flutter, Dextrocardia. Myocardial damage. Extra systoles. Inversion P, QRS and T waves in lead I. Slurring and notching of QRS complex.

The blood pressure was 120/60 in both arms

Abdomen There was a lower right paramedian scar, but no masses, tenderness, or rigidity. The liver dulness was on the left side. The spleen and kidneys were not palpable.

Extremities Pitting edema was present in both ankles and feet.

Laboratory data Blood hemoglobin, 86%, red blood cells, 4,550,000, white blood cells, 7,600, 81% polymorphonuclears, 17% lymphocytes, 2% monocytes. Urine yellow color; acid reaction, specific gravity, 1.015, negative for sugar, negative for acetone.

Progress notes April 29, 1931 Patient has had 26 cc of tincture of digitalis since entering the hospital. She has headaches and feels nauseated. Coupled beats are present.

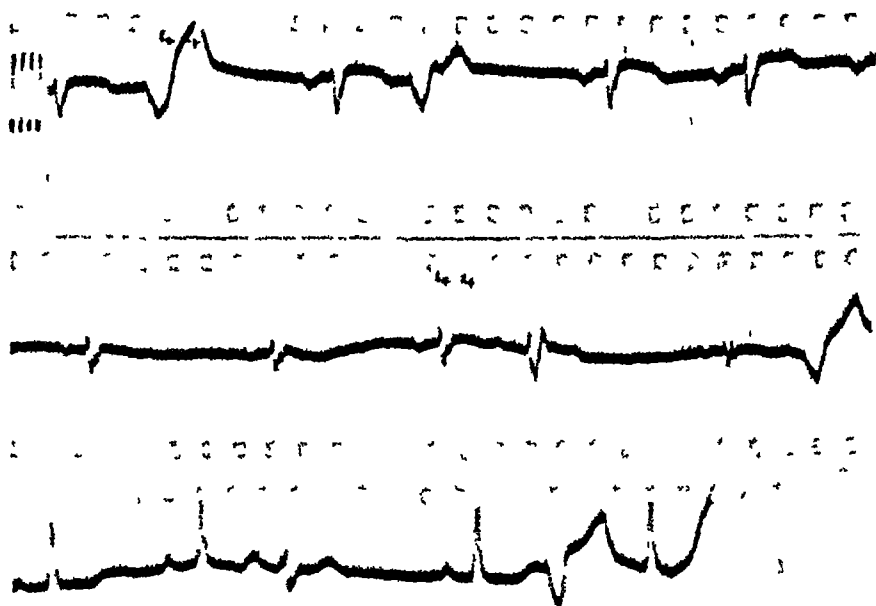
May 1, 1931 Ringing ears and headache from quinidine. (See table for medication.)

May 4, 1931 Heart slow and fibrillating, but well compensated. The patient wished to go home, and was discharged with tincture of digitalis, twenty minims three times daily. No symptoms of overdigitalization were present.

X-ray reports (Dr. Reynolds). April 28, 1931 Definite dextrocardia with slight enlargement of the cardiac shadow, heart occupying a transverse position. The lung fields are clear.

April 30, 1931 Fluoroscopic study of the chest shows a definite dextrocardia, the apex of the heart being almost in contact with the thoracic wall, indicating definite enlargement of the cardiac shadow. A small quantity of opaque meal was administered, which shows the stomach on the right side and the liver on the left. This is conclusive evidence of a situs transversus.

The patient was seen at intervals after discharge from the hospital, but not as often as advised because of poor cooperation. As soon as she felt comfortable she neglected treatment. She was advised rest in bed, light diet, and tincture of digitalis, fifteen minims three times a day. On September 21, 1931 she stated that she had taken



4 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

DIGITALIS AND QUINIDINE

DATE	MEDICATION	AMOUNT	TIME	PULSE RATE	NOTES
April 27, 1931	Tr Digitalis	drams 2	10 a m	60	
	Tr Digitalis	drams 1	2 p m	68	
	Tr Digitalis	drams 1	6 p m	60	
April 28, 1931	Tr Digitalis	drams $\frac{1}{2}$	8 a m	56	
	Tr Digitalis	drams $\frac{1}{2}$	12 noon	60	
	Tr Digitalis	drams $\frac{1}{2}$	4 p m	58	
	Tr Digitalis	drams $\frac{1}{2}$	8 p m	58	
	Tr Digitalis	drams $\frac{1}{2}$	8 a m	88	Nausea and headache
May 1, 1931	Quinidine	grs 6	9 a m	48	
	Quinidine	grs 6	12 noon	50	
	Quinidine	grs 6	4 p m	46	
May 2, 1931	Quinidine	grs 6	9 a m	52	Ringings ears
	Quinidine	grs 6	1 p m	48	Ringings ears, headache
May 3, 1931	Tr Digitalis	mm 20	6 p m	52	
	Tr Digitalis	mm 20	8 a m	46	
	Tr Digitalis	mm 20	12 noon	42	
	Tr Digitalis	mm 20	4 p m	42	

no medication for two weeks, and complained of return of symptoms as before. She was advised to remain in bed and continue digitalis. She was seen at intervals thereafter. While she was well compensated and went about with comfort, the auricular fibrillation and flutter were still present. In November, 1931, she decided to return to Roumania against advice. Soon after arrival there she was placed in a hospital and expired January 20, 1932.

The electrocardiographic depiction is a combination of auricular fibrillation and flutter, severe myocardial change and dextrocardia. The evidence for complete situs transversus comes from physical examination and is verified by x-ray findings which are conclusive. The electrocardiographic curves could be readily explained by mitral stenosis

with right ventricular preponderance and auricular fibrillation or impure flutter. For this reason the findings are very interesting, for no other instance of this particular combination is known to the author.

SUMMARY

1 This case is reported because of the very interesting combination of dextrocardia with auricular fibrillation and flutter.

2 With this combination a diagnosis based upon electrocardiographic evidence alone would be mitral stenosis with right ventricular preponderance and auricular fibrillation or impure flutter.

3 There is no case report in the literature of this particular combination.

A Medical Poet of the Middle Border, William Savage Pitts, M.D.

By LOUIS H. RODDIS, *Lieutenant Commander, Medical Corps,
United States Navy*

THERE are numerous English and American poets whose works are voluminous and who like Shakespeare, Milton, Byron and Longfellow are as notable for the quantity as for the quality of their verse. On the other hand there are not a few who owe their fame to almost a single song. Such are Gray with the "Elegy Written in a Country Churchyard", Cooke whose "Florence Vane" has been translated into more modern languages than there are verses in the poem, Lady Scott's "Anne Laurie", Foster's "Swanee River", and Payne's "Home, Sweet Home". In these latter the wedding of words and music has given the verses a double charm and to this fact at least some of their popularity is due.

Dr. Pitts was one of these poet-composers whose fame rests upon a single poem united with an air not soon forgotten. His song, "The Church in the Wildwood", has immortalized a little weathered frame church in a tiny Iowa village, has

made it the rival of the Little Church Around The Corner in respect to the number of weddings held there, and leads nearly a hundred thousand people to visit the locality annually. Something about the country doctor who wrote the poem and the circumstance under which it was produced may be of interest.

William Savage Pitts was born at Lums Corners, Orleans County, New York, August 18, 1830. His parents came to Wisconsin when he was a boy. His medical training was obtained at Rush Medical College in Chicago where he received his degree in medicine in 1868. After 1862 he had made his home in Fredericksburg, Iowa, and he returned there to begin the practice of medicine. In a short time his buggy was a familiar sight on the roads of Chickasaw County around Fredericksburg, Nashua, New Hampton, and Bradford. One of his old buggies is still in use on a farm near Fredericksburg. He was a great lover of horses and always had several fine animals. One of his favorites was a bay mare with white markings named "Blond". He drove her for many years through daylight and dark, and both day and night. He expressed his regard for her on a horse note.

Fredericksburg, Iowa, July 2, 1912.
The following is a copy of the original manuscript of the poem "The Church in the Wildwood" as written by Dr. William Savage Pitts. It is preserved in the collection of the Iowa Historical Society, Des Moines, Iowa.

mare is just like one of the family" She was then twenty-one years old

Dr Pitts was a typical country doctor of the old school, the friend and counselor of the community as well as a physician, known to the whole countryside, their help in times of accident and sickness, birth and death. The country doctor in farming communities of the middle west in those early days saw many hardships. Called at all hours and in all weathers, to make long drives over the worst of roads, to meet all sorts of medical, surgical and obstetric emergencies with poor facilities and untrained assistants, without professional consultation and encouragement, the old country doctors had to be men with physical, mental, and moral stamina, to meet their tasks and accomplish them with credit. That they usually were such men and that they did perform well the difficult duties of their calling is well known to millions who were their patients. With our refined methods of diagnosis, our laboratories and x-rays, we are apt to disparage their diagnostic methods, but necessity sharpened their powers of observation to such an extent that in the field of physical diagnosis, particularly in inspection and palpation, they were probably vastly superior to our present generation of medical men. Some of their homely therapeutics are also not to be despised. Bread and milk, and flaxseed poultices were not bad dressings for the pre-incisional stage of cellulitis and the rubbing of the chest with camphorated oil and swathing in flannel gave comfort and encouragement, at least in acute pulmonary conditions. We often overlook the fact in our more scientific

methods that comfort and encouragement are valuable healing agents. Liberalunctions of goose grease made babies of the last century fat and healthy even though nothing was known of fat soluble vitamins. As a matter of fact goose grease ununctions and cod liver oil, both commonly used by the country doctors of the older generation, were going completely out of style until the discovery of vitamins brought them into use again. A hot footbath with a little mustard or a little bran in the water, a hot lemonade with a little whiskey in it, five grains of quinine or Dover's powder, and a nice warm bed are still as good treatment for a severe cold at its onset as any that we ourselves with all our laboratory training have to offer.

If the country doctor had many hardships there were many compensations as well. The position of helper in times of distress and suffering, and of holder of that vast body of confidential information that even the religious confessional does not receive gave him a unique place. He was one of the leading men in the community, probably the most respected and looked up to person in it. He always had the best that the place afforded. His compensation in money might not be munificent but it was ample, and where money was not available and he was paid in kind, the choicest garden truck, potatoes, wood, butter, cheese, bacon, ham, quarters of beef, halves of hogs, poultry, head cheese, country sausage, buckwheat honey, and other similar commodities went to his door. His home was usually the best in town. This was true of Dr Pitts. His large white house is still standing in Fred-

to build a church I will not take time to tell of the trials, the disappointments and the successes that followed, suffice it to say, by the early winter of 1864, the building was ready for dedication

"While I was holding the singing school, near its close in the spring, the class went one evening to the church. It was not then seated, but rude seats were improvised. My manuscript of the song I had brought with me from Wisconsin had never been sung before by anyone but myself. I sang it there. Soon afterwards I took the manuscript to Chicago, where it was published by H. M. Higgins. It won a speedy recognition locally and with years won its way into the hearts of the people of the world. Soon after its publication the church at Bradford which had been painted brown, (for want of money to buy better paint, some say) became known as 'The Little Brown Church in the Vale.' My hope is that it will stand for a thousand years and call the Old Man and his descendants to worship.

"Under the circumstances, what more natural than that the little church at Bradford, Iowa, painted brown, and the song, 'The Lit-

tle Brown Church in the Vale' should be wedded and known as one and the same. Some people may try to rob the little church of its fame, but as long as it stands it will be known as 'The Little Brown Church in the Vale.'"

This is the song as Dr. Pitts wrote it and as he first sang it in the newly erected "Church in the Wildwood"

There's a Church in the valley by the wild-wood,

No lovelier place in the dale,
No spot is so dear to my childhood,
As the Little Brown Church in the vale

O, come, come, come, come,

Come to the Church in the Wildwood,
Come to the Church in the dale,
No spot is so dear to my childhood,
As the Little Brown Church in the vale

How sweet on a bright Sabbath morning,
To list to the clear ringing bell,
Its tones so sweetly are calling,
O, come to the Church in the vale

There, close by the Church in the valley,
Lies one that I loved so well,
She sleeps, sweetly sleeps, 'neath the willows,
Disturb not her rest in the vale

There close by the side of that loved one,
'Neath the tree where the wild flowers bloom,
When the farewell hymn shall be chanted,
I shall rest by her side in the tomb

It is thus seen that the writing of the song preceded the building of the church. As Dr. Pitts states, the poem was written in 1857. The church was not begun until 1859, and not completed until 1864. Bradford, the site of the church is now deserted, but in the early 1850's it was a place of some note, was an early Indian trading point, the first county seat of Chickasaw County, and on the stage line west toward Des Moines and Council

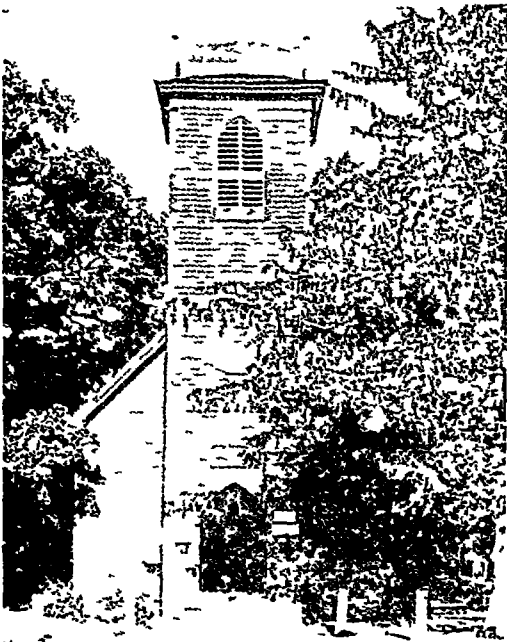


FIG 2 The Little Brown Church near Nashua, Iowa

stands, is deserted and falling to pieces

But if the town declined, the church did not, and as its fame grew, more and more people began to visit it and to come there to be married. Finally in 1900 a Society for the Preservation of the Little Brown Church was organized. A pastor was assigned from the Congregational Church of Nashua and for a number of years has held both charges. Now the church in the abandoned town has become the more important of the two, with thousands of visitors and a reputation as a matrimonial Mecca. Today each new bride married in the Church in the Wildwood has the privilege of ringing the famous old bell and that it is heard pretty frequently is shown by the fact that in 1929 six hundred and forty-three couples were married there. Three hundred and twenty-one couples were married there during the first six months of 1930. On January 16, 1926, thirteen couples pronounced their marriage vows before the altar. In front of the pulpit is a little square of green carpet. This has many times been worn out and replaced. The old Bible on the altar, however, is still unchanged. An inscription on the flyleaf shows that it was presented to the church by Mrs. Mary Vinton in 1864.

The present pastor, the Reverend William Kent, has learned the marriage ceremony by heart through frequent repetition and well deserves the title of "The marrying Parson of the Middle West." Every state in the Union and many foreign countries are represented by the long chain of brides and grooms. Iowa, Minnesota, Wisconsin, the Dakotas, Nebraska, Kan-

sas, and Montana furnish the greater number. Naturally enough Iowa leads the list and the largest number are always from the state "where the tall corn grows." Brides of the Middle West seem to take special pleasure in placing "Little Brown Church in the Vale" on their wedding announcements.

A register book is kept for visitors. More than thirty thousand have registered in a year and it is estimated that nearly as many visit the church without registering. It is believed that as many as one hundred thousand people make a pilgrimage to the spot annually.

The old bracket lamps in the church and the pews are as when first installed. On the reed organ a hymn book is always open at the "Little Brown Church in the Vale", and the singing of this song is a feature of every service. On the wall is a framed copy of the verses. The bell still calls the congregation to worship, and lovers to the holy bonds of matrimony. On Sundays during the summer months the little church is too small to hold the crowds that gather under the oaks and pines that embower it and make it still "the Church in the Wildwood."

In 1916 there was held a special reunion at the church at which Dr. Pitts, then aged 87, and the Reverend J. K. Nutting, aged 84, were present so that the writer of the song and the builder of the church were brought together again after a lapse of nearly sixty years. A picture of them was taken standing side by side in the doorway of the church. Each delivered a short address and Dr. Pitts sang the

song he had written fifty-nine years before

Dr. Pitts died in a hospital in New York City, September 25, 1918

In his later years he had made his home with a son, William Stanley Pitts in New York His death which was due largely to the infirmities of age followed a brief acute illness He is buried in the beautiful Rose Hill Cemetery in Fredericksburg, Iowa, where a small stone marks his grave

The following is a list of his poems None except the Church in the Wildwood had other than local fame and a number were never published and exist only in manuscript

"Little Fred"

"The Church in the Wildwood" or
"The Little Brown Church in the
Valley"

"Sabbath Bells"

"Nellie Wildwood"

"The Old Musician and his Harp"

Some others not now known

One cannot but ask what there is about this simple poem to enable a country doctor to immortalize and make world famous a little church in an obscure deserted town To answer that question one has but to listen to it sung by a pleasing voice or to read it over to oneself It is to be said that it possesses that magic yet indescribable charm of hymns certain lyrics linger in the memory and in the heart when

more pretentious poetry by greater poets is forgotten. The simple yet charming imagery of the "Valley in the Wildwood" and the appeal to the feelings common to all human nature such as the longing for immortality and the desire even in death to remain united with those loved in life are other reasons for its universal appeal Though his fame rests on a single song we may well add William Savage Pitts to the long and distinguished roll of medical poets.

BIBLIOGRAPHICAL NOTE

The Reverend Wm Kent, the present pastor of the First Congregational Church at Nashua, furnished much information in regard to the life of Dr Pitts and a number of pamphlets about the church and the poem A good feature article on the subject appeared in the *Minneapolis Tribune* of October 3, 1926 Lieutenant H R Hubbard, Supply Corps, United States Navy, who spent his boyhood in Fredericksburg told me Dr Pitts and his family, supplied many facts Mrs Ida Stiles of St Paul, who as a girl lived in Chickasaw County remembered Dr Pitts as their family physician When a young woman she sang in the choir of the Little Brown Church and she has contributed information of interest Dr Pitt's daughter Mrs Alice M Tuttle of Riverbank, California, has read the article in manuscript and made a number of comments and corrections Two other of Dr Pitt's children are here Mr Kate P Noble of Denver, Colorado, and William Stanley Pitt of New York City



Editorials

PROGRAM OF THE SEVENTEENTH ANNUAL CLINICAL SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS

Although the program of the Annual Clinical Session, which is to be held in Montreal, February 6 to 10, has been sent through the mails to all Fellows and Associates of the College, it is printed in the present issue for the added convenience of members and non-members alike. Those expecting to attend will find it very much to their advantage to study this program in advance. Attention is invited to the significant groupings of the subjects in the General Sessions, and particularly to the emphasis which is placed upon the intrinsic constitution as a factor in

determining disease. Those registering should plot their course in advance in respect to the Special Clinics and Demonstrations, some twenty-five of which are simultaneously available each morning. The necessity for early registration of choice and the wisdom of requiring clinic tickets will be apparent to all. It is to be hoped that many will avail themselves of the opportunity to visit the Library of the Medical School of McGill University, the Osler Library, and the Medical Museums at the McGill Medical Building and the Pathological Institute.

MAURICE CHARLES PINCOFFS, EDITOR OF THE ANNALS OF INTERNAL MEDICINE

It is with mingled feelings of regret and pleasure that the present editor of the *ANNALS* records the fact that his official duties end with the present number. There is regret like that at parting with a very close friend, or, as a better figure, with a member of one's own body, for it is impossible to edit, single handed, such a journal as the *ANNALS* without its becoming in a very real sense identified with one's self. There is regret at the loss of that stimulus, based on the ever-recurring necessity of surveying a long list of original papers and of periodi-

cals and books each month. And especially is there regret that the sequence of old and new contacts made each year with hundreds of authors and investigators, scattered over the continent is to be broken. Of the cooperation, forbearance, courtesy, and friendship of his authors, the editor is fully appreciative. With all of this, however, there is a sense of satisfaction in being able to announce that by the unanimous choice of the Regents of the American College of Physicians, Maurice C. Pincoffs, Professor of Medicine and Head of the

Department of Medicine, University of Maryland, Baltimore, Maryland, is assuming the editorship of the ANNALS. For three months there has been a gradual shifting of the editorial duties from the old office to the new so that there will be no interruption in the sequence of issues.

Doctor Pincoffs was born in Chicago in 1886, and received his elementary education in private schools in that city and in Antwerp. At the University of Chicago he earned the degree of Bachelor of Science and there he completed the first two years of the medical course, during which he was awarded the Brainard prize in Anatomy. He assisted in Anatomy for one year and took special courses in Pathology under Professor Gideon Wells. The medical degree he obtained from Johns Hopkins Medical School in 1912. Dr. Pincoffs was unusually fortunate in respect to the men with whom he was closely associated in his early years in Medicine. As interne, resident, associate, and voluntary assistant, respectively, he worked with Doctors James B. Herrick, Thomas R. Baggs, Lewellys F. Barker, and John J. Abel. From 1917 to 1919 he was in military service with the British Expeditionary Force, the American Expeditionary Force, and the American Expeditionary Force.

He served at Johns Hopkins Medical School as Instructor in Medicine from 1919 to 1922, assuming the full professorship in Medicine in the University of Maryland in 1922. He is also Physician-in-Chief of the University Hospital and of Mercy Hospital. Elected as a Fellow in 1923, Dr. Pincoffs has served the American College of Physicians as Governor, Regent and First Vice President. In addition to numerous articles in medical journals and transactions, he is the author of the section on Diseases of the Peritoneum in the Oxford System of Medicine, on Visceroptosis in Tice's System, and on Diseases Due to Chemical Agents in Musser's Internal Medicine. Thus Doctor Pincoffs, through training and experience in clinical medicine and medical education, is peculiarly fitted for the position for which he has been chosen. The ANNALS OF INTERNAL MEDICINE and the American College of Physicians are to be congratulated upon his selection and acceptance, which forecast continued success and added prestige for the official journal. May we bespeak for him the same loyal support which has been given his predecessor!

Abstracts

Abstracts of the literature of internal medicine, surgery, gynecology, and pediatrics, published in the English language, are included in this section. The abstracts are prepared by the editorial staff of the ANNALS OF INTERNAL MEDICINE, and are published in the ANNALS OF INTERNAL MEDICINE, Vol. 1, No. 1, 1923, pp. 1-100. The abstracts are published in the ANNALS OF INTERNAL MEDICINE, Vol. 1, No. 1, 1923, pp. 1-100. The abstracts are published in the ANNALS OF INTERNAL MEDICINE, Vol. 1, No. 1, 1923, pp. 1-100.

tennis, fewer formed elements and less albumin are found than after long distance cross-country running and hockey. Even after short periods of time in the lordotic posture, the excretion of blood cells is noted. In all of these tests white blood cells were found more frequently than red blood cells, and the latter more often than casts. Any condition which tends to concentrate the urine and increase its acidity may be responsible for an increase of formed elements. The medical practitioner should be on his guard not to attribute the presence of these formed elements, in the urine of normal persons, to pathological conditions.

The Hematopoietic Response in Pernicious Anemia Following the Intramuscular Injection of Gastric Juice By ROGER S. MORRIS, M.D., LEON SCHIFF, M.D., GEORGE BURGER, M.D., and JAMES E. SHERMAN, M.D. (Am Jr Med Sc, 1932, clxxxiv, 778-782)

The results of previous researches have seemed to indicate that the normal stomach secretes a substance (probably the same as that which Castle has shown to be present) which, while without effect on the reticulocytes when administered orally, might cause a response if it could be administered parenterally. This assumption has been tested by the intramuscular injection of neutralized sterile gastric juice and also of a concentrate of normal human gastric juice obtained by evaporation *in vacuo*. The results prove the presence in normal gastric juice of a powerful bone marrow stimulant, producing not only a marked and very rapid reticulocyte increase after intramuscular injection but also a rapid maturation of the red cells. For this anti-anemic substance, which is probably a hormone, the name *addisin* is proposed. This active principle, lack of which in the gastric juice would seem to be the cause of pernicious anemia, is found in the supernatant fluid, but not in the precipitate, which forms in the process of concentrating gastric juice. It is thermolabile, dialyzable, and exhaustible. Acetone extracted gastric juice of swine has been found to give less marked local and general reactions than the preparations first used.

Diathermy in the Treatment of General Paralysis and in Wassermann-Fast Syphilis By JAY FRANK SCHAMBERG, M.D., and THOMAS BUTTERWORTH, M.D. (Am Jr Syph, 1932, xvi, 519-534)

Under malarial therapy for paresis, about one-third of the patients go into a good remission, one-third into a partial remission, and one-third show no improvement. The average mortality with malarial therapy is about eight per cent. The authors have treated 26 cases of refractory syphilis by means of fever produced by diathermy. Of nine paretics who completed the treatment, six, or 66 per cent, improved, three returned to their former occupation. The single case of taboparesis treated showed marked improvement as did also the one case of cerebrospinal syphilis. Of the three cases of tabes dorsalis, one was relieved of his pains entirely and improved physically, a second patient improved physically, his pains decreased, but there was no improvement in his ataxia, the third became progressively worse. The two cases of interstitial keratitis showed considerable improvement, but in both, diathermy was augmented by mercurial inunctions and bismuth intramuscularly. Seven patients with Wassermann-fast syphilis showed no change in their serologic findings after treatment, although only one to seven months had elapsed since their discharge from the hospital.

Liver Function in Hyperthyroidism By S. S. LIGHTMAN, M.D. (Arch Int Med, 1932 1, 720-729)

Clinical evidence of disturbance of the liver in hyperthyroidism is afforded by occasional cases of icterus in association with thyrotoxicosis for which no other cause can be discovered. Hepatic changes, even a fully developed interlobular cirrhosis, have been discovered in some cases of hyperthyroidism. Thyroid substance, or thyroxin, causes the glycogen to disappear from the liver. The author investigated the liver function in a series of twenty consecutive cases of hyperthyroidism making use, among other methods, of an original cinchophen oxidation test. A disturbance in the oxidation of cinchophen was demonstrated in 16 of the 20 cases, the

results indicating moderate rather than severe impairment of the capacity of the liver to oxidize this substance. No apparent relationship between the degree of functional impairment of the liver and the basal metabolic rate, the known duration of the disease, or the percentage of weight lost was found. In individual cases, however, there appeared to be a tendency for the function of the liver cells to improve as the basal metabolic rate returned to normal. The galactose tolerance test gave no indication of a disturbance of hepatic function. There was little evidence of appreciable disturbance of the excretory functions of the liver as determined by studies on the icterus index, bilirubinemia, urobilinuria and urobilinogenuria.

Effect of Dietary Calcium and Phosphorus on Toxicity of Lead in the Rat. Rationale of Phosphate Therapy By DAVID H. SHERRING, (Proc Soc Exp Biol and Med, 1932, xxx, 248-254)

The rationale of the use of calcium compounds in the treatment of lead poisoning depended upon the following facts. First, the solubility of lead phosphate was found to be analogous to that of calcium phosphate, hence it was believed that lead might be deposited in bones in the same manner that bone salts are. Second it was believed that the deposition of lead in the bones could be reversed by furthering the process of calcification through the administration of calcium. Third the group action of lead could be neutralized by the administration of phosphate. It was thought to add additional evidence that calcium alone had no effect. It was thought that this could be proved by reference to the fact that the administration of calcium alone did not prevent the deposition of lead in the bones. It was thought that the administration of calcium alone did not prevent the deposition of lead in the bones. It was thought that the administration of calcium alone did not prevent the deposition of lead in the bones.

and phosphorus in the dietary make it seem obvious that the addition of calcium to lead diets which contain an inadequate amount of phosphorus does not lead to improved deposition of either calcium or lead phosphate in the bones, but, on the contrary inhibits such a process. If the aim of therapy in lead poisoning is to deposit lead, or to excrete it in an insoluble, and hence innocuous, form, an abundance of phosphorus or of foods containing phosphorus should be supplied. The correctness of this assumption was tested experimentally in rats. Eight groups of animals were fed 15 gm per cent of $2PbCO_3 \cdot Pb(OH)_2$ with and without the addition of either $CaCO_3$, Na_2HPO_4 , or $MgCO_3 \cdot Mg(OH)_2$. Four of the groups received the respective diets with, and four without, the addition of viosterol. In the group not receiving vitamin D, weight and longevity were most adversely affected in the sub-group receiving lead and magnesium compounds, with decreasing effects, in order, in those receiving calcium and lead compound, lead compound alone, and lead and phosphate. In fact, those receiving Na_2HPO_4 with lead gained weight steadily and appeared normal. With the exception of those in the Na_2HPO_4 group, which lived and did well, all of the animals receiving vitamin D died sooner than the corresponding controls not receiving the vitamin. It may be that vitamin D diverted calcium phosphate into the bones and allowed lead phosphate combined with phosphate, to circulate freely, whereas in the Na_2HPO_4 group the phosphate was adequate for deposition and excretion of both calcium and lead as phosphate. It would seem therefore that phosphorus is a control for the deposition of lead and that subsequent deposition could be accomplished by depositing lead in a relatively insoluble phosphate.

Reviews

Internal Medicine, Its Theory and Practice

Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P. 1316 pages, illustrated. Lea & Febiger, Washington Square, Philadelphia, 1932. Price, \$10.00, net.

The appearance of a new single-volume text book of medicine is always an event of importance in the field of medical publication. The text book of medicine is the corner stone in the building of a medical student's clinical library. It is probably more frequently referred to by the general practitioner than any other book. The consultant will read it to see what progress he may have overlooked in subjects that are not included in his special interests. There is no medical book which, if successful, will be more widely read than such a text book and none which may exert a greater influence in its generation on the level of medical practice.

The text books of recent years tend to be national in character rather than personal. Osler's text book was Osler and the experience of Osler's clinic. Cecil's text book is a summary of American medicine as Prie's is of British medicine. In this new volume Musser has brought together what might be called the medicine of American Medical Schools. The authors, including the editor, are all active teachers of medicine of professorial rank in the leading medical schools of the country. The restriction of the number of contributors to twenty-seven has allowed each one to cover completely a relatively large and relatively autonomous section of internal medicine. The reviewer feels that these sections have thereby gained something of a personal quality and a certain sense of perspective not otherwise attainable. This is, of course, particularly true of such sections as those on mental diseases and on gastro-intestinal diseases in both of which a perspective and an individual point of view are especially

desirable. Most of the authors have introduced their subject by a general discussion in which they have summarized the common features of the group of diseases to be described—their etiological factors, their pathologic physiology and, in some instances, their relative social importance. These introductions add greatly to the value of the volume. Many are models of concise clear statement of essential known facts. In future editions similar introductions might well be added to those chapters in which they are lacking.

The book is divided into four parts. Part I deals with the infectious diseases. The diseases of bacillary, coccal, virus, rickettsial, spirochetal, protozoal, metazoal and unknown etiology are dealt with in separate chapters. This is a logical arrangement. It also seems wise to have made an exception to this order in grouping in one chapter the contagious diseases of childhood. It is less easily understood why the subject of tuberculosis should be omitted from this part of the book and dealt with only under the heading of pulmonary tuberculosis. There are few criticisms to be made of these excellent chapters on the infectious diseases. The treatment of the important subject of lobar pneumonia seems too summary. In discussing the pneumococcus types only the first three and group IV are mentioned. No statement is made of possible harmful effects from digitalis. The use of concentrated sera is dismissed with the statement that Cole has said that whole horse serum is superior.

Part II covers the systemic diseases. The chapter on diseases of the heart and pericardium is clear, well proportioned, and conservative. The etiological types of heart disease are well presented, and the various valve lesions and arrhythmias are separately discussed. An equal level of excellence is maintained in most of the other chapters.

The presentation of the diseases of the endocrine glands is especially concise and informative. In the otherwise admirable chapter on the respiratory diseases the brief and inadequate account of empyema seems regrettable. Certain of the blood diseases also receive scant consideration. A surprising clinical picture of agranulocytosis is presented, certainly not that most commonly seen.

Part III is devoted to diseases of nutrition, allergy, metabolism, physical and chemical agents. These chapters are clear summaries of the more important aspects of the disease processes concerned. It is perhaps unavoidable that most of the space is given to description of the chemical, physical, metabolic and immunological backgrounds, and that the clinical descriptions are correspondingly brief.

Part IV is on diseases of the nervous system. These are dealt with in two chapters. The first on mental disorders covers this field somewhat more thoroughly than is usual in text books of medicine. The psychoses are divided into those associated with organic disease, those of toxic origin, and the functional psychoses. The limited space devoted to the chapter on the organic diseases of the nervous system has resulted in a very brief discussion of many of them. The pages given to anatomy and methods of examination could be utilized to better advantage in amplifying the clinical descriptions. It is customary to include a brief discussion of anatomy and methods of examination in a chapter on neurological diseases but in reality it is no more appropriate than it would be to insert a general discussion of physical diagnosis or of clinical pathology in the other sections of the book. The inclusion of a discussion of level of vision and the explanation given under each of the sections are excellent features.

At the end of the book may be offered a few criticisms. The book is too large for a text book of medicine. It is too expensive. The book is too large for a text book of medicine. It is too expensive. The book is too large for a text book of medicine. It is too expensive.

Accidents, Neuroses and Compensation By JAMES H. HUFFLSON, M.D., Associate in Neurology, Columbia University, and Attending Neurologist, Neurological Institute, New York, with a Foreword by J. RAMSAY HUNT, M.D., Sc.D., Professor of Neurology, Columbia University, ix + 256 pages. Williams and Wilkins Co. Baltimore, 1932. \$4.00.

The passing of each year is accompanied by a startling increase in the legal and medical perplexities revolving about essentially psychogenic disorders resulting from or associated with physical injuries. With the steady growth of various and conflicting types of industrial compensation laws, these problems have established themselves among the most difficult ones with which the medical profession must contend. They represent a boundary zone in which honesty and knavery are most intimately mingled and keen indeed must be the physician's analysis if he is to insure justice for patient and employer. The author approaches his problem fortified by a broad background of experience replete with illustrative material. From his contact with that richest of all sources of traumatic neuroses, the World War, he is able to contribute substantially to the understanding and rationalization of many forms of neurosis. The book follows the usual form of special disease presentation; etiology, symptomatology and diagnosis, pathology, therapeutics and prophylaxis are discussed in a systematic manner. The treatment of the subject is in some respects encyclopedic, the varied theories and conceptions concerning each important point being presented in a condensed manner with complete references to the literature. For the purely diagnostic reader is amplified so that the reader can find at once the book in this part. The book is to the casual reader, the author's style is excellent. It is to be hoped that the book will be widely read and that the author's suggestions for the treatment of these cases will be followed. The book is a valuable addition to the library of every physician who deals with the problems of accidents, neuroses and compensation.

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Throughout the work, the legal aspects of this medical problem are emphasized and especial stress is given the relationship between the duration and character of compensation and the severity of the disease. The direct relationship between the duration of the neurosis and the time span and expectancy of compensation forms a medico-legal association which would well justify the presentation of this volume to every judge, lawyer or commission dealing extensively with workmen's compensation and industrial insurance. Forty pages are devoted to bibliography, which with the index, constitutes nearly one-sixth of the book. This high proportion is almost necessitated by the nature of the material presented, for without these divisions, in their complete form, much of its usefulness as a reference work would be lost.

J C B

Treatment of Syphilis By JAY F SCHAMBERG, A B, M D, Professor of Dermatology and Syphilology in the Graduate School of Medicine of the University of Pennsylvania, former President of the American Dermatological Association, etc and CARROLL S WRIGHT, B Sc, M D, Professor of Dermatology and Syphilology in the Temple University School of Medicine, Associate Professor of Dermatology and Syphilology in the Graduate School of Medicine of the University of Pennsylvania, former President of the Philadelphia Dermatological Society, etc xxiv + 658 pages, 62 illustrations D Appleton and Company, New York and London, 1932 Price, \$8 00

To those who appreciate the complexity of the problems arising in the management of syphilis and at the same time are aware of the incidence of this disease, a book of generous size on the *treatment* of syphilis need occasion no surprise. It is believed with good reason that the 200,000 cases of syphilis which are reported annually to Public Health authorities in this country represent not more than one-fifth or one-fourth of those actually under medical care each year. In addition there are the other

tens, and probably hundreds, of thousands who remain undiagnosed, or if diagnosed, are not receiving treatment. There is no practitioner nor specialist into the field of whose endeavors syphilis does not obtrude. The authors of this book believe that 15 to 20 per cent of chronic invalids in the wards of general hospitals are there because of the chronic effects of syphilis upon the internal organs. A comprehensive survey of present knowledge and experience in the management of this disease is to be welcomed. While the authoritative position of the authors in their special field would entitle them to *ex cathedra* utterance, they have given full recognition to the opinions of others. Thus an analytical survey of the entire field is presented. The clinical illustrations are well chosen but not always as well reproduced as they deserve. Little need be added as to scope of the contents of this book. It is in every respect adequate. Full discussion of "cured" syphilis and of the ever-recurring question of syphilis and marriage is provided. It is a pleasure to recommend this thoroughly scholarly book to all interested.

A Descriptive Atlas of Radiographs An Aid to Modern Clinical Methods By A B BERRWISTLE, M D, Ch B, F R C S Ed Second edition, revised and enlarged xxviii + 552 pages, 767 illustrations C V Mosby Company, St Louis, 1932 Price, \$13 50

There are many text-books and monographs for those who are specializing in Radiology, but few which are sufficiently fundamental and yet broad enough in scope to serve the needs of those who are engaged in general or special practice but who are not themselves radiologists. For such the need of sufficient knowledge to be able to understand the interpretations of others and, on occasion, to form worthwhile judgments of their own, is obvious. An extended chronology of the outstanding achievements in radio-diagnosis serves as an historical introduction. The illustrative plates, with short clinical and descriptive notes make up almost the entire volume. Plates of normal structures are placed on left hand pages and those of pathological

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Minor criticisms which may be offered do not affect the estimate of the book as a whole. It is a valuable presentation of the present status of our knowledge of internal medicine. It is unusually readable and stimulating. The reviewer feels that it can be highly recommended to students, to teachers, and to practitioners of medicine.

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conditions on right hand pages only. Thus confusion is avoided and comparison facilitated. The first 57 figures are of normal skeletal structures, and include an exposition of silhouette radiographs, combining the advantages of demarcation of the soft parts with adequate detail in the bone. Congenital abnormalities are represented by 15 figures, fractures, by 99, inflammatory disease of bone, by 79, neoplasms of bone, by 27, injuries and diseases of joints, by 61, the nasal and dental regions with related structures, by 45, the alimentary system, by 171, the urinary system, by 51, the respiratory system, by 72, the nervous system, by 50, the vascular system, by 12, the thyroid system, by 8, the female generative system, by 8, and the muscles, by 11. Much of interest and value to the medical man who is not a "radiologist" can be found in this book.

Fungous-Diseases. A Clinico-Mycological Text. By HARRY P. JACOBSON, M.D., Attending Dermatologist and Member of the Malignancy Board, Los Angeles County General Hospital. With Introductions by JAY FRANK SCHAMBERG, M.D., Professor of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, and HOWARD MORROW, M.D., Clinical Professor of Dermatology, University of California Medical School. xiv + 317 pages, 153 illustrations. Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland. 1932. Price, \$5.50, postpaid.

Clinical mycology is presented by Jacobson with emphasis on the clinical aspect. Thus the major divisions of his book are based upon the character of the disease process, rather than upon a botanical classification. Division A is for the "primary cutaneous mycoses with (usually) no definite systemic involvement." This includes the ringworms and related condition. Division B includes the "primary cutaneous and or mucous membrane infections with frequent systemic involvement." Under this heading are found moniliasis, maduromycosis, sporotrichosis, blastomycosis, actinomycosis, and coccidioidal granuloma. The third division, C, for torulosis and asper-

gillosis, is characterized as "primary systemic infections with occasional instances of skin or mucous membrane involvement." The author writes from an extensive and rich experience. The subjects treated do not include all of the mycotic diseases of man of this country, but, as is evident from the foregoing lists, all of the important ones and some of the less common are presented. The clinical and bacteriological illustrations are good, those of histopathologic features are not particularly informative. This is sure to prove an extremely useful book to both practitioners and laboratory workers, for it brings together a large material much of which was hitherto available only in original sources.

A Guide to Human Parasitology for Medical Practitioners. By D. B. BLACKLOCK, M.D. (Edin.), D.P.H. (London), D.T.M. (Liverpool), Professor of Parasitology, Liverpool School of Tropical Medicine, the University of Liverpool, formerly Director of the Sir Alfred Lewis Jones Laboratory, Freetown, Sierra Leone, West Africa, and T. SOUTHWELL, D.Sc., Ph.D., A.R.C. Sc., F.Z.S., F.R.S.E., Lecturer in Helminthology, School of Tropical Medicine, Liverpool, formerly Director of Fisheries to the Government of Bengal, and Bihar and Orissa, Scientific Advisor and Inspector of Pearl Banks to the Ceylon Company of Pearl Fisheries, and Honorary Assistant, Zoological Survey of India. viii + 271 pages, 2 colored plates and 122 illustrations. William Wood and Company, New York, 1932. Price, \$4.00.

A Guide to Human Parasitology is intended as a guide for a medical practitioner who has had no experience in the subject and the studies are made with such simple equipment as anyone practicing medicine could have at hand. Sources of material for practice are suggested and the importance of good preparations is stressed in these words, "the making of good blood or feces films is half the battle." The microscope and its use is explained in considerable detail, a point which scarcely seems necessary to the average present day medically trained person. Inspection of the table of contents at once reveals that the authors have arbi-

trarily limited the scope of their subject to the spirochetes and the animal parasites of man. This should be shown in the title as its present form is highly misleading. Are the pathogenic bacteria any less "parasitic" than the protozoa? More than half of the book is devoted to parasitic worms. Numerous charts and figures illustrate the diagnostic characters of the worms and their pathogenicity to man. The discussion of human trichinosis is inadequate for the needs of practitioners in this country. There is no mention of the cardiac complications, of the finding of larvae in the cerebrospinal fluid, or of the value of biopsy of muscle in doubtful cases. Clever "pictographs" are used to make clear the complete life-history of the infecting organism. To the student these graphic presentations must prove of very great value. A few pages on myiasis follow. Near the end of the book is included an outline of treatment with a table of dosage for the diseases mentioned previously, and also a list of apparatus and chemicals needed in the study of parasites. This Guide is worth reading and will be useful to anyone particularly interested in parasitic worms. The charts and illustrations, particularly the "pictographs," add much to this book. Whether treatment should be taken up in such a brief manner is a question.

R. C. W.

A Handbook of Experimental Pathology. By GEORGE WAGONER, M.D., Associate in Pathology, and R. PHILIP CUSTER, M.D., Associate in Research Medicine, The School of Medicine, University of Pennsylvania. Foreword by Professor EDWARD BELL KRUMBHAAR. Illustrations by ERWIN F. FABER. xv+160 pages, 22 illustrations. Charles C. Thomas, Springfield, Illinois, 1932. Price, \$4.00 postpaid.

A handbook dealing with the materials and methods of experimental pathology is timely for its aids in steering a course between utter neglect of this important aid to the study of the nature of disease on the one hand and ill-advised experimentation on the other. Throughout, care is taken to give methods which cannot be subject to deserved criticism as inhumane. After a very

useful section on the housing and management of animals, technical methods are described in a general way and tables of normal blood findings in laboratory animals are provided. More than one hundred experiments in general and special pathology are described with stimulating questions and selected references for most of them. The illustrations of apparatus serve their purpose, but those showing the microscopical appearances of tissues are unsatisfactory. This book, the outgrowth of five years' experience, will prove a useful guide to teachers and students seeking to develop a dynamic conception of the processes of disease in the living body.

Diseases of the Thyroid Gland with Special Reference to Thyrotoxicosis. By CECIL A. JOLL, M.S., B.Sc. (Lond), F.R.C.S. (Eng.); Senior Surgeon to the Royal Free Hospital and the Miller General Hospital; Surgeon to the Cancer Hospital; Consulting Surgeon to the Royal Buckinghamshire Hospital; Late Hunterian Professor, Royal College of Surgeons. xviii+682 pages, 284 text figures, 24 colored plates. C. V. Mosby Company, St. Louis, Missouri, 1932. Price \$20.00.

One wonders, in advance of examination of the book, at the temerity of the American distributors of this very expensive English text on diseases of the thyroid. Have we not felt that we have kept a little ahead of our colleagues in Great Britain in this very field of investigation? Close scrutiny of the book itself explains the venture. Although we may differ with the author on various questions, and particularly regret that he has not given fuller consideration to the constitutional pathology of Graves' disease, we recognize in Joll's treatise an orderly and well digested compilation of a huge material. Lack of recognition of the probable significance of lymphoid tissue in the thyroid is revealed by a glance at figure 12 which is labeled "normal thyroid gland" although it shows a "lymphorrhage". The acceptance of the conception of lymphadenoid goiter has similar significance. Critical analysis of the many chapters is impossible here. The numerous illustrations and particularly the fine

colored plates explain the relatively high cost of this volume. As an important reference book this monograph should be in every medical library and at the disposal of all who are especially concerned with diseases of the thyroid gland.

Oral Spirochetes and Related Organisms in Fusio-Spirochetal Disease. By DAVID T. SMITH, A.B., M.D., Associate Professor of Medicine, Duke University, School of Medicine, Durham, N. C.; formerly Bacteriologist and Pathologist to the New York State Hospital for Incipient Tuberculosis, Ray Brook, N. Y. xii+243 pages; 53 illustrations. The Williams and Wilkins Company, Baltimore, 1932. Price, \$4.50.

"There is no evidence either clinical or experimental that the oral spirochetes alone can produce disease in man. But they are probably the most important member in a symbiotic group of anaërobic organisms which is capable of initiating a severe and often fatal disease. The first five chapters of this book deal with the biological characteristics of the mouth organisms. These are followed by presentation of the clinical aspects of the morbid states with which the fusio-spirochetal complex is associated. These are grouped by regions. While reference to the association of these conditions, and particularly the anginal group, with various pathological states of the blood is made, it would seem to be timely to give more emphasis and attention to the problem of granulocytopenia. Numerous historical references add interest; treatment is adequately considered, and a bibliography of 822 items (but without titles) brings this excellent monograph to a close. It is an important and useful text for clinicians, pathologists and laboratory workers.

An Introduction to Dermatology. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (Edin.), Professor of Diseases of the Skin, University of Kansas School of Medicine; and RICHARD L. SUTTON, Jr., A.M., M.D., Visiting Dermatologist to the Kansas City General Hospital. xvi+565 pages, 183 illustrations. The C. V. Mosby Company, St. Louis, 1932. Price \$5.00.

This abridged text in dermatology is based on the eighth edition of *Diseases of the Skin* by the senior author. It is intended primarily for the student, and gives him the essential material requisite for his knowledge without that huge mass of information found in the larger texts, much of which is useful only to the specialist. The abridgement has been accomplished, not by the omission of diseases, but by reducing the general descriptions, the discussions, and statistical material. The illustrations are very well selected for their value in differential diagnosis, and are well reproduced. The book has a certain freshness of style and directness of approach which commend it most strongly. It should prove of great value to the practitioner as well as to the medical student

Diabetes in Childhood and Adolescence. By PRISCILLA WHITE, M.D., F.A.C.P., Physician at the New England Deaconess Hospital, Boston, Massachusetts. With a Foreword by ELLIOTT P. JOSLIN, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital; Physician at the New England Deaconess Hospital, Boston, Massachusetts. xiv+236 pages, 25 engravings and a colored plate. Lea & Febiger, Philadelphia, 1932. Price, \$3.75.

Over 500 living cases of diabetes in the juvenile age period formed the basis of the material in this book. Throughout, the thesis is developed that the *living* diabetic child is the most outstanding medical accomplishment of the past decade. From nearly 100 per cent the mortality of diabetes in childhood has dropped nearly to the vanishing point. All phases of diabetes and of the physiology of the diabetic child are considered. The treatment of the disease itself and of its common complications is fully set forth. Not the least interesting is the chapter giving the present physiological, economic and social status of 76 diabetic children who have survived ten or more years. This book deserves a sympathetic reception and careful study. It reflects energetic study, achievement of a high order, and optimism.

A Text-book of Pathology. By W. G. MAC CALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Fifth edition, thoroughly revised. xvi+1212 pages, 652 illustrations, many in color. W. B. Saunders Company, Philadelphia and London, 1932. Price, \$10.00.

A new edition of MacCallum's well-known textbook requires no introduction nor any explanation of its worth. Well-written, well-illustrated and well-printed, this work has been maintained at a high level of excellence by frequent revisions. For student and clinician alike it continues to provide a highly satisfactory foundation in the principles of general and special pathology. "A constant effort has been made to speak of the disturbances of function and of chemical interchange in the course of disease, as far as that was possible, and even to describe symptoms. If this makes the book seem like a treatise on clinical medicine, it is only because pathology and clinical medicine are, after all, the same thing viewed from slightly different angles."

The Sputum: Its Examination and Clinical Significance. By RANDALL CLIFFORD, M.D., F.A.C.P., Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School; formerly Associate Physician and Director of Pulmonary Clinic, Massachusetts General Hospital. xx+167 pages, 21 text figures and 7 plates in colors. The Mac-Millan Company, New York City, 1932. Price, \$4.00.

Clifford's book is a complete practical guide to the collection and study of the sputum. Macroscopic and microscopic features, technical methods of examination, and methods of disinfection of the contents of the sputum cup are given in satisfactory detail. About fifty pages are devoted to a discussion of the character and clinical significance of the sputum in some twenty of the more common diseases of the bronchi and lungs. Both the black and white figures and the colored plates are well chosen and well reproduced. This book can be confidently recommended to students and practitioners.

Die Ernährung des Herzens und die Folgen ihrer Störung. [The Nutritional Mechanism of the Heart, and the Results of Interference with It.] Ergebnisse der Kreislaufforschung, Band III. By Dr. Med. Luigi Condorelli, Professor in the University of Naples. xii+230 pages, 70 illustrations, in part colored. Theodor Steinkopff, Dresden and Leipzig. 1932. Price, in paper, R M 18.80; bound, R M 20.00.

This monograph is divided into four major parts. The first describes in full the anatomy of the coronary circulation and of the lymphatics of the heart. In the second there is a broad treatment of the physiology of the vessels of the heart, including the effects of various drugs. The third chapter deals with the experimental pathology of the coronary system. In this section is included much original work by the author on modifications in the electrocardiogram following infarction of known areas in the myocardium. The final division presents the pathology in man associated with coronary disease, including the less well known forms of coronary arteritis. Each section has an extensive bibliography.

Experimental Pharmacology and Toxicology: A Selected Laboratory Course. By HENRY G. BARBOUR, A.B., M.D., Yale University, New Haven, Connecticut. 141 pages, 14 illustrations. Lea & Febiger, Philadelphia, 1932. Price, \$2.75, net.

Barbour's manual presents a selected laboratory course in pharmacology based on twenty years of experience. Naturally, its field of interest will be found to be largely restricted to teachers of this subject. It is a neat, well printed book, interleaved in blank for the taking of notes, and presents more than forty well chosen experiments.

Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1932. vi + 199 pages.

United States Government Printing Office, 1932. For sale by the Superintendent of Documents, Washington, D.C. (Treasury Department Document No. 5053). Price, \$1.00 (cloth).

College News Notes

AMENDMENTS TO THE BY-LAWS

The Board of Regents of the American College of Physicians submits herewith recommended amendments to the By-Laws, to be acted upon by the Fellows and Masters at the next Annual Business Meeting, Montreal, February 9, 1933.

The purposes of these amendments are:

1. To make the Editor of the official journal of the College an *ex officio* member of the Board of Regents;
2. To provide for a single Committee on Credentials, consisting of three appointees from the Board of Regents and three appointees from the Board of Governors, in order to promote unity in the application of admission standards and in, order to simplify the procedure for the election of Associates.

It is, therefore, recommended that the following articles, or sections thereof, shall be amended to read as follows (*italics indicate insertions or changes*):

BY-LAWS, ARTICLE II, Section 1

"The Board of Regents shall consist of *twenty-four* members as follows: The President, the President-Elect, the Vice-Presidents, Secretary-General, Treasurer, Chairman of the Board of Governors, *Editor of the official journal*, and fifteen members elected from among the Masters and Fellows."

BY-LAWS, ARTICLE II, Section 4

"The Board of Regents shall appoint *three* members to *serve on the* Committee on Credentials whose duty it shall be to pass upon the qualifications of those proposed for Fellowship or Associateship, and recommend those considered eligible to the Board of Regents. *This Committee shall consist of six members, three appointed by the Board of Regents and three appointed by the Board of Governors, in such manner as to provide for continuity of service, with not more than one new member each year from each Board.*"

BY-LAWS, ARTICLE IV, Section 2

"The Board of Governors shall meet in executive session annually at the time and place of the annual meeting of the American College of Physicians for the transaction of such business as may come before it." (*Omit balance of paragraph.*)

BY-LAWS, ARTICLE IV, Section 6

"The Board of Governors shall appoint *three* members to *serve on the* Committee on Credentials whose duty it shall be to pass upon the qualifications of those proposed for Fellowship or Associateship, and recommend those considered eligible to the Board of Regents."

BY-LAWS, ARTICLE V, Section 3 (c), paragraph 4

"The credentials of candidates for Fellowship shall be considered first by the Committee on Credentials, which Committee shall report to the Board of Regents for election, deferment or rejection."

BY-LAWS, ARTICLE VI, Section 2, sentence 2.

" After 1931, he may be required to present himself for personal examination, the character of which shall be determined by the Committee on Credentials."

"The credentials of candidates for Associateship shall be considered first by the Committee on Credentials, which Committee shall report to the Board of Regents for election, deferment or rejection."

BY-LAWS, ARTICLE VI, Section 3, paragraph 2, sentence 2

" At the expiration of three years, he shall be notified in writing by the Committee on Credentials of his eligibility for election to Fellowship during the next two years, provided he shall meet within that time the requirements necessary for Fellowship. If not elected to Fellowship within five years, his Associateship will automatically cease."

Respectfully submitted,

COMMITTEE ON CONSTITUTION
AND BY-LAWS
Sydney R. Miller, Chairman
Alfred Stengel
S. Marx White

Abstracts of Minutes of the Meeting of the
BOARD OF REGENTS

Philadelphia, Pa.
November 13, 1932

The Board of Regents of the American College of Physicians met at the College Headquarters in Philadelphia at 11:00 A.M., November 13, and was presided over by Dr. F. M. Pottenger, President.

Those present included Dr. F. M. Pottenger, Dr. George Morris Piersol, Dr. Maurice C. Pincoffs, Dr. Charles G. Jennings, Dr. William D. Stroud, Dr. William Gerry Morgan, Dr. Walter L. Biering, Dr. George E. Brown, Dr. John H. Musser, Dr. O. H. Perry Pepper, Dr. James S. McLester, Dr. Jonathan C. Meakins, Dr. James H. Means, Dr. James Alex. Miller, Dr. Sydney R. Miller, Dr. David P. Barr, Dr. James B. Herrick, Dr. Clement R. Jones, Dr. S. Marx White and Dr. W. Blair Stewart. Dr. Charles H. Cocke, Dr. Ernest B. Bradley, members of the Committee on Credentials, and Dr. Alfred Stengel and Dr. Charles F. Martin, members of special Committees, were present as guests. The Executive Secretary, Mr. E. R. Loveland, acted as Secretary of the meeting.

The Executive Secretary read abstracted minutes of the meetings of the Board of Regents held at San Francisco, April 4-8.

The resignation of Dr. William Gerry Morgan, dated April 7, 1932, as a member of the Board of Governors was read, and upon motion regularly adopted, the resignation was accepted, in view of the fact that Dr. Morgan is now the Secretary-General of the College.

Eighteen special cases of members of the College, concerning illness, inability to pay dues, change of status, etc., were reviewed by the Secretary-General, Dr. Morgan, and individual action taken.

The resignations of five Fellows and two Associates were read by the Executive Secretary, and discussed by the Regents. Upon motion by Dr. McLester, seconded by Dr. Biering, and regularly adopted, it was

RESOLVED, that action on the resignations of the members named be postponed until the Montreal meeting in view of the fact that the dues of the College are to be reduced and some of these members may desire to continue their memberships.

The Executive Secretary announced the following deaths, which had been reported since the last meeting of the Board of Regents:

Fellows:

Byron Fuller Barker, Bath, Maine	April 29, 1932
Ray Carrington Blankinship, Madison, Wis.	August 23, 1932
A. J. BurrIDGE, Winnipeg, Man.	March 15, 1932
Luther C. Davis, Fairmont, W. Va.	September 5, 1932
Charles Joseph Durand, Colfax, Calif.	July 6, 1932
Elmer H. Funk, Philadelphia, Pa.	May 13, 1932

Alfred Leftwich Gray, Richmond, Va.	October 13, 1932
William C. Heussy, Seattle, Washington	March 21, 1932
John A. Lichty, Clifton Springs, N.Y.	May 2, 1932
Charles G. Lucas, Louisville, Ky.	July 7, 1932
Frederick Wilmot Mann, Houlton, Maine	June 16, 1932
Orlando H. Petty, Philadelphia, Pa.	June 2, 1932
James Manara Rector, Columbus, Ohio	September 17, 1932
Lorraine Schwartz, Pittsburgh, Pa.	July 25, 1932
Benjamin F. Shuttleworth, Clarksburg, W. Va.	March 31, 1932
Leonard F. C. Wendt, Detroit, Mich.	June 11, 1932

Associates:

Edwin Massie Bell, Allenwood, Pa.	August 20, 1932
Charles Rollin Grandy, Norfolk, Va.	June 10, 1932
Alexander B. Kalbaugh, Westernport, Md.	May 15, 1932
Joseph W. Malone, Brooklyn, N.Y.	September 10, 1932
George Henry Sherman, Detroit, Mich.	April 19, 1932

On motion by Dr. White, seconded by Dr. James Alex. Miller, it was

RESOLVED, that the Secretary-General shall prepare appropriate resolutions for Dr. John A. Lichty, Dr. Charles G. Lucas and Dr. Elmer H. Funk, as past members of the Board of Regents, said resolutions to be submitted at the next meeting of the Board of Regents.

Letters by Dr. William J. Kerr, Dr. J. N. Hall, Dr. G. Gill Richards, Dr. James R. Arneill and Dr. C. T. Burnett, concerning the time of our Annual Clinical Sessions with regard to date were presented. A resolution was adopted that these letters be received.

Dr. E. A. Broughton, of Toronto, and Dr. Harold E. Waxman, of Pittsburgh, were reinstated as a Fellow and an Associate, respectively.

The following candidates were regularly elected to Fellowship in the College:

Anderson, Edward Waldemar	Des Moines, Iowa
Cecil, Russell L.	New York, N.Y.
Fort, Wetherbee	Baltimore, Md.
Fox, Leon Alexander	Washington, D.C.
French, Harry T.	Hanover, N.H.
Gottlieb, Julius	Lewistown, Maine
Hamilton, James	Providence, R.I.
Hamilton, John Richard	Nassawadox, Va.
Kolmer, John Albert	Philadelphia, Pa.
Riven, Samuel Saul	Nashville, Tenn.
Schoenheit, Edward William	Asheville, N.C.
Swann, Walter Clifford	Huntington, W. Va.

The Executive Secretary was requested to report upon the financial operation of the College for the current year. He presented the comparative cost analyses of the ANNALS OF INTERNAL MEDICINE for Volumes III, IV and V, showing a great improvement in the financial status of Volume V over Volume IV, due to a reduction in the volume of the News Notes Section, due to an increase in circulation, and due to a reduction in printing cost. He pointed out, too, that his office has been able to maintain, in fact slightly to increase, the amount of paid advertising in the journal over previous years, in spite of the financial situation. He then presented a comparative cost analysis for conducting the last four Clinical Sessions, this statement disclosing that the San Francisco Clinical Session for the current year cost \$8,129.80 more than any previous Clinical Session, due to an increase in the traveling expenses of guest program speakers and members of the Board of Regents, and due, also, to certain increased local costs in San Francisco. In commenting on the other expenditures for 1932, he pointed out that the expenditures for his office had been reduced by securing a reduction of \$240.00 in rental for the Executive Offices, and by a re-

duction in the office staff of a secretarial assistant whose salary was \$1200.00 per annum. Other economies had also been put into effect, so that had we not had the increase in the cost of the San Francisco Clinical Session and the added expenses of the Phillips Memorial Prize, which in itself amounted to a total of \$1878.82, which had not been granted in previous years, the surplus for 1932 would be approximately as large as for any preceding year, in spite of the fact that the income from initiation fees has been reduced at least fifty per cent. The application of the new provision of the By-Laws requiring all new members to come in first as Associates eliminates at this time the larger initiation fees paid in previous years, the shrinkage in income from this source alone for 1932 amounting to approximately \$9000.00. It is estimated that there will be a surplus of income over expenditures at the end of 1932 of \$5587.52. The Executive Secretary further asserted that the salaries of his office staff were not above the present level. In fact, that in the case of his Secretary, he considered her underpaid.

Dr. William D. Stroud presented the Treasurer's report, including the following bank balances as of October 31, 1932:

On deposit in closed banks:

Bank of Pittsburgh	\$ 7,797.16	
Exchange National Bank, Pittsburgh	3,887.12	
Highland National Bank, Pittsburgh	6,627.51	\$ 18,311.79

On deposit in open accounts:

Colonial Trust Company, Pittsburgh	7,398.86	
Commonwealth Trust Co., Pittsburgh	989.62	
First National Bank, Pittsburgh	2,486.83	
Girard Trust Co., Philadelphia	21,770.96	32,646.27
		<u>\$ 50,958.06</u>

He recommended authorization by the Board of Regents to open an account in a Montreal bank for convenience in depositing Canadian checks and for the payment of Canadian bills during the period of the forthcoming Clinical Session. He further reported the elimination of practically all costs in conducting the Treasurer's office, since his assumption of the Treasurer's duties, due to the fact that he requires no secretarial assistance, such work being done in the Executive Secretary's office. His summarized report follows:

Endowment Fund, January 1, 1932	\$ 52,400.00	
General Fund, January 1, 1932	57,166.00	
		<u>\$109,566.00</u>
Income, January 1, 1932, to October 31, 1932	\$ 39,563.17	
Expenditures, January 1, 1932, to October 31, 1932	29,370.65	
	<u>\$ 10,192.52</u>	
Excess income over expenses, October 31, 1932	4,605.00	5,587.52
Estimated expenses for November and December, 1932		
This, plus Endowment Fund and General Fund of January 1, 1932, gives a total balance of		<u>\$115,153.52</u>

Dr. Stroud further reported that two of the closed banks had paid dividends during the year, and that the ex-Treasurer, Dr. Jones, had expressed the opinion that the closed banks in Pittsburgh, in which balances of College funds remain, would eventually pay the College in full.

Dr. Clement R. Jones, Chairman of the Finance Committee, then presented his report, which was freely discussed by all present. In connection with expenses, Dr. James Alex. Miller inquired concerning a control of the expenses of the annual meetings, and was informed that the expenses of the Executive Secretary only were budgeted and limited, and that there had been no budget control or recommendations for the General Chairman,

local committees and the President. Dr. Miller recommended that when the meeting place for 1934 is selected, the Finance Committee shall prepare a budget for the General Chairman and for the President, limiting the expenditures that may be made.

The following resolution was regularly adopted

- RESOLVED: (1) That the annual dues for Fellows shall be reduced to \$15.00, and of Associates to \$12.00, per annum, for the year 1933;
- (2) That the Treasurer shall recommend to the Finance Committee an additional depository in Philadelphia and one in Montreal;
- (3) That the securities of the College now held in Pittsburgh shall be transferred to a Philadelphia bank;
- (4) That the John Phillips Memorial Prize for 1933 be in the sum of \$1000.00, plus the expenses of the recipient to the Seventeenth Annual Clinical Session;
- (5) That the Treasurer shall be authorized to purchase with approximately \$1000.00, representing interest on securities now on deposit, a Government bond either of the United States or of Canada;
- (6) That \$50.00 per month for November and December shall be transferred from the Treasurer's budget for 1932 for the payment of secretarial services of the new Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Maurice C. Pincoffs;
- (7) That there be a temporary reduction in the salary of the Executive Secretary, of ten per cent as an estimated equivalent to the present reductions in costs of living, and that the matter of the reduction in the budget for his office staff be left to his discretion;
- (8) That the salary of the Editor of the ANNALS OF INTERNAL MEDICINE be reduced ten per cent per annum;
- (9) That the President-Elect be authorized to secure any appropriate reduction in rent;
- (10) That the Finance Committee following the selection of the meeting place each year be instructed to prepare a budget for the President and the local General Chairman, controlling the expenses for their respective programs.

Dr. James H. Means, Chairman of the Committee on the John Phillips Memorial Prize, reported that in accordance with the regulations governing the award of the Phillips Memorial Prize, his Committee had selected a candidate for 1933 and presented the following resolution, which was duly seconded and regularly approved by the Board:

RESOLVED, that the John Phillips Memorial Prize for 1933 be awarded DR. WILLIAM B. CASTLE, of Boston, for his series of studies showing the relation of gastric digestion to the pathogenesis of anemia, the demonstration of the rôle of extrinsic and intrinsic factors in hematopoiesis, and finally in the demonstration that the extrinsic factor in treating pernicious anemia can be obtained from yeast as well as meat, suggesting that it is closely related to vitamin B.

Dr. Maurice C. Pincoffs, Chairman of the Committee on ANNALS OF INTERNAL MEDICINE, reported that the Executive Secretary had assembled estimates from ten different printers, including the Ann Arbor Press, for printing the ANNALS OF INTERNAL MEDICINE, and that the estimates submitted disclosed that material saving could be made during the coming year, either by continuing with the Ann Arbor Press, who had submitted a lower price than that at which they are now printing the journal, or by changing the printers. In view of the desirability of keeping the present volume with the same format, arrangement, etc., and, further, in view of the fact that going on with the present printers would be an aid to him in the formative period of his Editorship, Dr. Pincoffs wished to recommend that the Ann Arbor Press continue to print the journal up to and including the June, 1933, number. His Committee had further considered certain changes,

such as the elimination of abstracts and the enlargement of book reviews; also the matter of the size of the type page and various other details which they felt might somewhat improve the journal. Dr. Pincoffs asked for an expression of opinion by the Board as to the obligation to print every paper presented on the General Program of the Annual Clinical Sessions, expressing the feeling that he felt it was not desirable so to do, but that the Editor should have the same privilege of selection as he has with the acceptance of papers from those submitted directly.

The following resolution was regularly adopted:

RESOLVED, that it is the sense of the Board of Regents that a statement be sent to each essayist on the General Program that there is a requirement of the Board that their manuscripts be submitted in completed form at the time of delivery at the meeting for consideration for publication by the Editor of the ANNALS OF INTERNAL MEDICINE.

Dr. Sydney R. Miller, Chairman of the Committee on Constitution and By-Laws, reported that three matters had been referred to his Committee for consideration in regard to amendments to the By-Laws:

- (1) The making of the Editor of the ANNALS OF INTERNAL MEDICINE an *ex officio* member of the Board of Regents instead of continuing a precedent of having the Editor continuously act as the First Vice-President of the College;
- (2) An amendment to the By-Laws in regard to a resolution adopted by the Board of Regents on April 6, 1932, and referring to a provision for the appointment of a Finance Committee of three from the Board of Regents to perform certain duties;
- (3) Advisability of amending the present provisions for two separate Committees on Credentials, and to provide for one Committee, consisting of three appointees from the Board of Regents and three appointees from the Board of Governors, with provision for the continuity of their service, and with an amendment to the By-Laws with respect to the method of election of Associates.

Dr. Miller reported that the first and third items, in their opinion, fully merited amendments to the By-Laws, but that the second item is unnecessary, since the present By-Laws, Article II, Section 3, fully provide that it is within the province and authority of the Board of Regents "to create, appoint and direct all standing Committees". His Committee recommended that the Board of Regents provide for a standing Committee of three members, appointed in such manner as to provide that one member shall retire each year, his vacancy being filled on appointment by the President, and that the Finance Committee shall be advisory, and its duties and powers defined from time to time by the Board of Regents.

RESOLVED, that the Board of Regents approves of the recommendations by the Committee on Constitution and By-Laws, and hereby instructs that Committee to prepare the detailed amendments and publication of same at least one month in advance of the next General Business Meeting in February.

Dr. Charles G. Jennings, Chairman of the Committee on Public Relations, reported the receipt of a number of communications asking for an investigation of the activities of Fellows of the College who are connected with certain groups, or clinics, which appear to be inconsistent with the ethical standards of the College. Cases also submitted dealt with group practice and contract medicine. The Committee recommended that the Board of Regents advise these correspondents that the College has no adequate method of determining the character of these criticized activities; and that the Board delay action upon them pending action by local medical bodies. The Committee on Public Relations further recommended that the Board of Regents suggest to the Committee on Credentials that it give full consideration to participation in these activities by applicants for membership in the College. The Committee considered, without formal action, questions in reference to abuses that may exist in the operation of the Veterans' Compensation Bureau and the Workingmen's Compensation Acts. Further information will be secured concerning the working of these bodies, in order that the Committee may be better prepared to consider them in the future. The report of the Committee was formally approved by the Board of Regents.

Doctors Pottenger and Meakins presented reports concerning the program for the Seventeenth Annual Clinical Session at Montreal.

Dr. James B. Herrick presented an invitation from all the grade A medical schools in Chicago, the Chicago Medical Society, the Illinois State Medical Society, the Chicago Association of Commerce, and the Mayor of Chicago, for the American College of Physicians to meet in the City of Chicago in 1934. The Board, as a body, expressed their appreciation of the invitation and assured Dr. Herrick that when the matter of the next meeting city is considered during the forthcoming Montreal Session, his invitation from Chicago will be most carefully considered.

The following resolution was regularly adopted:

RESOLVED, that the President appoint a member to fill the vacancy on the Committee on Credentials for Fellowship, due to the death of Dr. John A. Lichty.

President Pottenger announced the reappointment of Dr. W. Blair Stewart as a member of the Committee on Public Relations; his new term to terminate with the 1936 Session.

The following resolution was regularly adopted:

RESOLVED, that the President appoint Dr. James H. Means as the official delegate of the American College of Physicians to attend the International Goiter Conference at Berne, dependent upon the development of his plans to attend this Conference.

Adjournment.

At a recent meeting in Chicago, the directors of Alpha Omega Alpha Honor Medical Society adopted resolutions in recognition of the eminent services of the late Dr. William W. Root, Slaterville Springs, New York, the founder of the society and secretary-treasurer since its organization in 1902. The present officers of the society are Walter L. Bierring (Fellow), Des Moines, president; Austin A. Hayden, Chicago, vice-president; Josiah J. Moore (Fellow), Chicago, secretary-treasurer. Mrs. Root will continue as assistant secretary. In addition to the officers, the directorate includes Ray Lyman Wilbur, Washington, D.C.; Waller S. Leathers (Fellow), Nashville; Louis B. Wilson, Rochester, Minn., and Willard C. Rappleye (Fellow), New York City. The committee on extension and policy comprises Elias P. Lyon, Minneapolis, chairman; William Pepper, Philadelphia; Irving S. Cutter, Chicago; Frederick C. Waite, Cleveland, and Thomas C. Routley, Toronto.

Dr. Ray M. Balyeat (Fellow), Oklahoma City, addressed the 35th annual meeting of the Santa Fe Railway Medical and Surgical Society at Topeka, December 5, 1932, on "Allergic Diseases: With Special Reference to Symptoms Due to Allergy Simulating Surgical Conditions".

Dr. Herman B. Allyn (Fellow), Philadelphia, was made the guest of honor at the annual dinner of the Association of Ex-resident and Resident Physicians of the Philadelphia General Hospital, held at the Philadelphia Country Club on December 6, 1932. Dr. Allyn had been successively Interne, Registrar and Visiting Physician to the hospital, serving in all about thirty-five years. At the time of his retirement from active service he was President of the Medical Board of the Hospital. He is now Consulting Physician.

Doctor Wm. M. James (Fellow), Panama, is the author of two papers which have appeared in the Annual Report for 1931 of the Medical Department of the United Fruit Company. In this same volume there are also two papers by Doctor Ricardo Aguilar (Fellow), Quirigua, Guatemala; and a book review by Doctor Lawrence Getz (Fellow), Panama.

Doctor Julius Friedenwald (Fellow), Baltimore, has been elected President of the Baltimore City Medical Society for the year 1933-34.

Dr. David Riesman (Fellow), Philadelphia, delivered an address on "The Oldest Medical School in America" before the Society of the County of Kings in Brooklyn, New York, on December 20, 1932.

PROGRAM SEVENTEENTH ANNUAL CLINICAL SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS

Montreal, Can., February 6-10, 1933

Francis M. Pottenger, President
General Sessions

Jonathan C. Meakins, General Chairman
Clinical Program

E. R. Loveland, Executive Secretary
133-135 South Thirty-sixth Street
Philadelphia, Pa.

GENERAL AND HOTEL HEADQUARTERS: WINDSOR HOTEL,
Dominion Square, Montreal, Can.

LIST OF MONTREAL HOTELS

All Prices Are for Rates per Day, European Plan

<i>Windsor</i> (Headquarters)	(Capacity 610)
Single room without bath	\$2.50
Single room with bath	4.00
Double room without bath	4.00
Double room with bath	7.00
<i>Mount Royal</i>	(Capacity 1050)
Single room with bath	\$3.00 up
Double room with bath	6.00 up
<i>Ford</i>	(Capacity 750)
Single room without bath	\$1.50 to \$2.00
Single room with bath	2.00 to 2.50
Double room without bath	3.00 to 3.50
Double room with bath	4.00 to 5.00
<i>Queen's</i>	(Capacity 350)
Single room without bath	\$2.00 to \$2.50
Single room with bath	3.00 to 4.00
Double room without bath	4.00 to 5.00
Double room with bath	6.00 to 8.00
<i>Hotel De LaSalle</i>	(Capacity 250)
Single room with bath	\$3.00 to \$6.00
Double room with bath	4.00 to 7.00
<i>Ritz-Carlton</i>	(Capacity 218)
Single room with bath	\$4.00 up
Double room with bath	8.00 up
<i>Place Viger</i>	(Capacity 118)
Single room without bath	\$2.50 to \$3.50
Single room with bath	3.50 to 5.00
Double room without bath	4.00 to 6.00
Double room with bath	7.00 to 10.00

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1933 (dues, if not paid previously, may be paid at the Registration Desk).
- (b) All newly elected members.
- (c) Members of the Montreal Medico-Chirurgical Society, La Société Médicale, Montreal Clinical Society, L'Association des Médecins du Nord, L'Association des Médecins del l'Est and L'Action Médicale, without registration fee, upon presentation of their 1933 membership cards.
- (d) Medical students pursuing courses at McGill University and the University of Montreal, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions.
- (e) House Officers of the hospitals participating in the program, upon presentation of proper identification.
- (f) Members of the Medical Corps of Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.
- (g) Qualified physicians who may wish to attend this Session as visitors. Such visiting guests shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to "Annals of Internal Medicine" (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU.—Located in the Rose Room, Windsor Hotel. Hours: 8:00 A.M. to 6:00 P.M., daily, February 6-10.

REGISTRATION BLANKS FOR ALL CLINICS AND DEMONSTRATIONS are sent to members with the official program. Guests will secure registration blanks at the Registration Bureau during the Session.

TRANSPORTATION—A reduction to one and one-half fare for the round trip on the "Identification Certificate Plan" will apply for physicians and dependent members of their families.

Members are privileged to make the going journey by one route and return by another route. The fare for children of five and under twelve years of age will be one-half of the round trip fare for adults; children under five years of age free when accompanied by parents or guardian. Stop-overs will be allowed at all stations within final limit on either going or return trip, or both, on application to conductors.

Before purchasing tickets, members must secure from the Executive Secretary an Identification Certificate, to entitle them to the reduced fares.

In general, tickets will be sold from January 28 to February 10, depending upon the relative distance from Montreal, with a return limit of thirty days in addition to date of sale.

All tickets must be validated by a special railroad agent at the Montreal headquarters from February 6-10.

BANKING FACILITIES

Arrangements have been made with the Royal Bank of Canada to exchange money and cash cheques for the registered visitors to the Clinical Session. The Bank has made these special arrangements in their Branch at the corner of St. Catherine and Stanley Streets, which is two blocks removed from the Headquarters in the Windsor Hotel.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 4:30 P.M., Thursday, February 9, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary and the induction to office of the new President, Dr. George Morris Piersol, Philadelphia, Pa.

SPECIAL FEATURES

Monday, February 6, 1933

The John Phillips Memorial Oration will be delivered by Dr. William B. Castle, of Boston, Mass., at the evening General Session at 9 o'clock. After this a *Smoker* will be held in the Prince of Wales Salon of the Windsor Hotel. There will be a program of entertainment, and refreshments will be served. Members of the College, guests and visitors are cordially invited to attend, as it is hoped that this informal function will provide an opportunity early in the Session for members and guests to meet each other.

Tuesday, February 7, 1933

A Hockey Match between "The Canadiens" of Montreal and "The Maple Leafs" of Toronto, in the National Hockey League, will be played at the *Forum* (corner of St. Catherine Street and Atwater Avenue) at 8:00 P.M. A block of seats has been reserved for the Fellows and visitors, and tickets may be obtained at the Information or Registration Bureaus before 1:00 P.M., Tuesday.

Wednesday, February 8, 1933

CONVOCATION OF THE COLLEGE—8:00 o'clock, Windsor Hall. All Masters and Fellows of the College and those to be received in Fellowship should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to occupy the central section of seats especially reserved for them. As this is the most formal meeting of the College, it is urged that all appear in evening dress.

The Convocation is open to all physicians and their families generally, and to such of the general public as may be interested.

Following the Convocation Ceremony, the President of the College will present the John Phillips Memorial Prize for 1933 to Dr. William B. Castle, of Boston, Mass.

Sir Andrew MacPhail, Professor of the History of Medicine, McGill University, will deliver an address on "The Source of Modern Medicine."

The President, Dr. Francis M. Pottenger, of Monrovia, Calif., will then deliver the annual presidential address to the Masters, Fellows and Associates of the College.

The Presidential Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the interim between the Convocation and the Reception.

Thursday, February 9, 1933

THE ANNUAL BANQUET OF THE COLLEGE will be held at the Windsor Hotel at 7:30 P.M. All members of the College and its Officers, physicians of Montreal and visitors attending the Session, with their wives, are invited to be present at the Banquet.

Dr. Charles F. Martin will act as Toastmaster, and Dr. Stephen Leacock, William Dow Professor of Political Economy, McGill University, will deliver an address on "The Waste Spaces of Modern Education."

Tickets for the Banquet, \$5.00 per person, may be purchased at the Registration or Information Bureaus before 10:00 A.M., Thursday.

ENTERTAINMENT FOR VISITING WOMEN

A program has been arranged for the entertainment of the visiting women in attendance at the meeting, but ample time has also been allowed for individual excursions and shopping. Shopping lists, including the names of the principal shops, will be issued by the Local Committee for the Entertainment of Visiting Women.

POST-CONVENTION TOURS

In order that those attending the Session may have an opportunity of visiting historic Quebec City in its splendid winter garb and enjoy the winter sports, the railways will offer reduced week-end rates. In addition, the Chateau Frontenac Hotel, so beautifully situated

on the bold cliff overlooking the city and river, is making a special rate of seven dollars (\$7.00) a day, American Plan, for any who may wish to visit Quebec City on a post-convention trip.

Similar arrangements have been made with the Seignior Club at Lucerne-in-Quebec for the rate of eight dollars (\$8.00) a day, American Plan. The Seignior Club, Lucerne-in-Quebec, is built around one of the old French-Canadian seigneuries with buildings including the old Manor House, the Log Chateau (with accommodation for 300 members and guests), a year-round swimming pool and sports Club House. It is situated in the Laurentian Mountains, seventy-five miles from Montreal.

THE EXPOSITION AND COMMERCIAL EXHIBIT will be located in the Concourse and Rose Room of the Windsor Hotel, in close proximity to Windsor Hall, the meeting hall for the General Sessions.

Exhibits, consisting of medical literature and texts, pharmaceutical products, apparatus and appliances, special foods, etc., will be shown by leading American and Canadian publishers and manufacturers. These exhibits afford an opportunity for physicians to examine the latest literature and the newest products in the field of medicine generally; their educational value should not be overlooked. Every attendant at the Session is urged to visit each of the booths, for he cannot help but find something new, interesting and scientifically valuable. Intermissions in the general program have been arranged from Tuesday to Friday, inclusive, for the purpose of providing a definite time for the inspection of exhibits.

CLINICAL PROGRAM

Full advantage has been taken of the excellent facilities for clinical teaching which are afforded by the hospitals attached to the two Medical Schools in Montreal. It has been found possible to provide ample accommodation for the Clinical Session in eight places which are practically all within a short distance of the Headquarters. They consist of four large general hospitals, two pediatric hospitals, and the Biological Building, Pathological Institute, and Medical Building of McGill University. Daily bedside and theatre clinics have been arranged in all of these hospitals and demonstrations in the University buildings.

Medical Libraries—The Medical Library of McGill Medical School and the Osler Library, the gift of the late Sir William Osler, will be open to visitors daily, both morning and afternoon. There will be found in both a large collection of medical books, both ancient and modern. All who are interested in rare editions are advised to pay these libraries a visit.

Medical Museums—The Medical School of McGill University has for several generations been very rich in its museum collections. These are now housed at the McGill Medical Building and also at the Pathological Institute.

Special exhibits of "Congenital Heart Disease," Sir William Osler's collection of pathological specimens with their biographies which he compiled during his period as Pathologist at the Montreal General Hospital, and a collection illustrative of Medical History covering many parts of the world, will be arranged for daily inspection by the Fellows and visitors.

DEMONSTRATIONS AT THE MCGILL MEDICAL BUILDINGS

Demonstrations have been arranged in the laboratories of the Departments of Pharmacology, Biology, Physiology and Anatomy. These will cover the special work that is occupying the attention of these various departments and should interest many of the Fellows and visitors.

Clinico-pathological Conferences will be held each morning at the Montreal General Hospital. These conferences have been held for many years and hold a unique position in the medical activities of this institution.

At the Royal Victoria Hospital Professor Oertel will conduct the Conference, on Thursday morning. On the other mornings there will be demonstrations by the Staff of the Pathological Institute dealing with a variety of pathological subjects.

EXPERIMENTAL MEDICINE

In the laboratories of the University Clinic at the Royal Victoria Hospital there will be demonstrated each morning at 11 o'clock interesting results in various problems of Medicine.

PEDIATRICS

A varied program for those interested in Pediatrics has been provided at both the Children's Memorial Hospital and the Hôpital Ste. Justine. The symposia at the former institution on lead poisoning and rheumatic fever in childhood should be particularly attractive.

PSYCHIATRY AND NEUROLOGY

In addition to a number of clinics on neurological subjects, there have been arranged two symposia. One deals with the influence of emotional factors in organic disease, while the other is devoted to the problem of epilepsy.

GENERAL CLINICS

Many clinics have been arranged in cardiovascular, gastro-intestinal, pulmonary, and blood diseases, as well as diseases of the ductless glands and of metabolism.

There will be clinical symposia on diseases of the biliary passages, diabetes, goitre, collapse therapy in pulmonary tuberculosis, syphilitic cardiovascular disease, nephritis, and essential hypertension.

In addition to the small bedside clinics, larger ward clinics have been arranged by the Senior Members of the Staff at the Montreal General Hospital. At the Royal Victoria Hospital one ward has been set aside each day for the demonstration of interesting cases. The Fellows and visitors are invited to visit these wards at their leisure when they may examine and discuss the problems they present with members of the Staff.

GENERAL SESSIONS

In preparing the program for the General Sessions we have attempted to make it reflect the best work that is being done in medicine. The place which the College holds in the minds of medical men can well be estimated from the ready response of those invited to present papers. The response on the part of those who were able to attend the meetings was almost 100 per cent. While the contributors come from various parts of the country it was necessary in constructing the program this year to bear in mind the deterrent effect of long journeys.

There are several features of the program which require emphasis.

That physiological studies are coming more and more to the fore in medical work will be emphasized by the fact that there is a thread of physiology both normal and pathological running through most of the discussions in this program.

Constitutional factors of both an anatomical and physiologic nature will be discussed. The physiological activity of the cell will be presented from both a theoretical and practical standpoint. The difference in chemical constitution favorable to various diseases and the manner in which diseases may be influenced by altering body chemistry will be dwelt upon.

The place of the two correlating mechanisms of the body—the chemical in the form of hormones, and the nervous as represented by both the somatic and visceral nervous systems—is discussed, and the relationship of these systems to normal and pathological function will be stressed.

Endocrinology—A special feature is the symposium on endocrinology, in which the papers will be presented by investigators to whom we are indebted for original work in the particular field discussed. With the new work which is being brought out in this field many of the enigmas of metabolism, growth and development are now being solved, and the body reactions heretofore inexplicable are now being understood.

The Nervous System—Neurology and the psychical side of medicine will be stressed in several important papers dealing with problems of both an organic and functional nature. Epilepsy and schizophrenia will be treated from special standpoints. The part which the autonomic nervous system plays in disease will be presented in practical form.

Pulmonary diseases will be discussed from several angles. Tuberculosis will be presented from the standpoint of the internist as well as the specialist. The suppurative lesions of the chest will be presented by our distinguished French guest and by America's pioneer chest surgeon. The lung will also be discussed from the standpoint of being a focus of systemic infection.

The Heart and Arterial System hold the attention of medical men in a special manner, because of their increased morbidity now that so large a percentage of people are living beyond middle life. Angina pectoris will be treated from both the medical and surgical aspects. Papers on electrocardiography, endocarditis, valvular lesions, the effect of hyperthyroidism on the heart and pulsus alternans will be presented.

Lesions of the peripheral vascular system will be presented. The fact that these affections have recently been treated more or less successfully by operative procedure, based on a better understanding of vascular neurology, adds an ever increasing interest to the subject.

Miscellaneous Subjects—The rôle which sensitization plays in immunity is an important and fascinating subject, and will be presented in an authoritative manner. There will also be discussions of the so-called allergic diseases, diabetes, diseases of the blood, diseases of the pancreas and liver, neurosyphilis, and other problems which are met daily by clinicians. The history and philosophy of medicine will be presented by a paper on the Source of Modern Medicine.

The John Phillips Memorial Prize Oration will be given on Monday evening by William B. Castle, of Boston, for his series of studies showing the relationship of gastric digestion to the pathogenesis of anemia, the demonstration of the rôle of extrinsic and intrinsic factors in hematopoiesis, and finally in the demonstration that the extrinsic factor beneficial in pernicious anemia can be obtained from yeast as well as meat suggesting that it is closely related to Vitamin B.

Through the courtesy of the Provincial Government we are especially fortunate in having a distinguished Parisian physician participate in our program.

OPENING GENERAL SESSION

Monday Afternoon, February 6, 1933
2:00 o'Clock

WINDSOR HALL

1. Addresses of Welcome:

The Honourable L. A. Taschereau, K.C., Premier of the Province of Quebec.
The Honourable Fernand Rinfret, Mayor, City of Montreal.
Charles F. Martin,† Dean, Faculty of Medicine, McGill University.
L. de L. Harwood, Dean, Faculté de Médecin, Université de Montréal.

2. Response to Addresses of Welcome:

F. M. Pottenger,* President of the American College of Physicians.

3. The Diagnostic Use of Iodine in Thyrotoxicosis.

James H. Means,* Boston, Mass.

4. Irradiation Treatment of Hyperthyroidism.

George E. Pfahler,* Philadelphia, Pa.

5. Some Aspects in Cell Physiology.

W. J. V. Osterhout, New York, N.Y.

(Guest)

6. The Effect of Vitamins and the Mergonic Elements on the Growth and Resistance to Disease in Children.

Alan Brown, Toronto, Ont.

(Guest)

†M.A.C.P. *F.A.C.P.

7. A Study of the Ultra Violet Rays in the Western and Southwestern Portions of the United States.
Meldrum K. Wylder,* Albuquerque, N.M.

SECOND GENERAL SESSION
Monday Evening, February 6, 1933

8:00 o'Clock

WINDSOR HALL

1. Spontaneous Versus Artificial Regulation of Constitution for the Control and Prevention of Disease.
Millard Smith, Boston, Mass.
(Guest)
2. The Rôle of Desensitization in Recovery from Bacterial Infections.
William B. Wherry, Cincinnati, Ohio.
(Guest)

9:00 o'Clock

JOHN PHILLIPS MEMORIAL PRIZE ORATION
"The Etiology of Pernicious Anemia and Related Macrocytic Anemias."
William B. Castle,* Boston, Mass.

10:00 o'Clock

SMOKER
Prince of Wales Salon

THIRD GENERAL SESSION
Tuesday Afternoon, February 7, 1933
2:00 o'Clock

WINDSOR HALL

Presiding Officer

Jonathan C. Meakins,* Montreal, Que.

1. Treatment of Polycythemia Vera.
Ernest Falconer,* San Francisco, Calif.
2. Polycythemia Associated with Pulmonary Disorders
James J. Waring* and W. B. Yegge,* Denver, Colo.
3. The Platelets and Platelet Volume in Blood Dyscrasias.
H. Z. Giffin* and K. K. Nygaard, Rochester, Minn.
4. Observations on Addison in Diseases of the Blood.
Roger S. Morris,* Cincinnati, Ohio.
5. Anatomy and Physiology of the Cerebral Circulation.
Stanley Cobb, Boston, Mass.
(Guest)
6. The Patient as a Person.
A. H. Gordon, Montreal, Que.
(Guest)
7. The Influence of Diets High in Fat upon the Insulin Treated Cases of Diabetes.
Henry Rawle Geyelin, New York, N.Y.
(Guest)
8. Lower Fat Diet in Diabetes.
Joseph H. Barach,* Pittsburgh, Pa.

9. Complications of Diabetes.
Lea A. Riely,* Oklahoma City, Okla.
10. Gastro-intestinal Allergy in Children.
Horton Casparis,* Nashville, Tenn.
11. Clinical Observations on Some of the Causes, Organic and Other, of Abdominal Pain and Distress.
S. Franklin Adams,* New York, N.Y.

FOURTH GENERAL SESSION

Tuesday Evening, February 7, 1933
8:00 o'Clock

WINDSOR HALL

Presiding Officer

David Preswick Barr,* St. Louis, Mo.

1. Carbohydrate and Fat Metabolism.
C. H. Best, Toronto, Ont.
(Guest)
2. The Biochemistry and Physiology of the Follicular Hormone.
E. A. Doisy, St. Louis, Mo.
(Guest)
3. Studies on the Function and Clinical Use of Cortin.
Frank A. Hartman, Buffalo, N.Y.
(Guest)
4. Physiology of the Anterior Pituitary and Relationship of Pituitary to Placental Hormones.
J. B. Collip, Montreal, Que.
(Guest)
5. Therapeutic Use of Placental Hormones.
A. D. Campbell, Montreal, Que.
(Guest)
6. Differentiating the Functions of the Anterior Pituitary Hormones.
Oscar Riddle, Cold Spring Harbor, L.I., N.Y.
(Guest)
7. Effect of Hormones on Cellular Permeability.
Ernest Gellhorn, Chicago, Ill.
(Guest)

FIFTH GENERAL SESSION

Wednesday Afternoon, February 8, 1933
2:00 o'Clock

WINDSOR HALL

Presiding Officer

James Alex. Miller,* New York, N.Y.

1. Pulmonary Tuberculosis in General Practice.
Reginald Fitz, Boston, Mass.
(Guest)
2. Conservatism the Keynote in the Treatment of Tuberculosis.
Charles H. Cocke,* Asheville, N.C.
3. The Indications for Collapse Therapy in Pulmonary Tuberculosis.
Isidor David Bronfin,* Denver, Colo.

4. Reflections Concerning the Treatment of Chronic Purulent Bronchiectasis.
Edward W. Archibald, Montreal, Que.
(Guest)
5. Collapse Therapy of Bronchiectasis.
E. Rist, Paris, France.
(Guest)
6. The Rheumatic Lung.
C. P. Howard, Montreal, Que.
(Guest)
7. Hereditary Abnormalities and Constitutional Traits in Experimental Animals.
Wade H. Brown, New York, N.Y.
(Guest)
8. The Value of the Galactose Test in the Diagnosis and Prognosis of Intrahepatic Icterus.
George Morris Piersol,* Philadelphia, Pa.
9. The Differential Diagnosis of Diseases of the Liver and Spleen by the Aid of Roentgenography after Intravenous Injection of Thorium Dioxide Sol.
Wallace M. Yater,* Washington, D.C.
10. Some Clinical Aspects of the Acid Base Balance of the Body.
Samuel M. Alter,* Los Angeles, Calif.
11. Radiotherm Therapy in Neurosyphilis.
Walter M. Simpson,* Dayton, Ohio.

ANNUAL CONVOCATION
Wednesday Evening, 8:00 o'Clock

WINDSOR HALL

The general profession and the general public are cordially invited. No special admission tickets are required. Evening dress is recommended.

1. Convocation Ceremony.
2. Address: "The Source of Modern Medicine."
Sir Andrew MacPhail, Montreal, Que.
3. Presentation of the John Phillips Memorial Prize.
4. President's Address.
F. M. Pottenger, Monrovia, Calif.

PRESIDENTIAL RECEPTION

The Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the interim between the Convocation and the Reception.

SIXTH GENERAL SESSION
Thursday Afternoon, February 9, 1933
2:00 o'Clock

WINDSOR HALL
Presiding Officer
Noble Wiley Jones,* Portland, Ore.

1. The Nervous Patient.
George C. Hale,* London, Ont.
2. Schizophrenia from the Physiological Point of View.
R. G. Hoskins, Boston, Mass.
(Guest)

3. The Evidence for a Cerebral Vascular Mechanism in Epilepsy.
Wilder Penfield, Montreal, Que.
(Guest)
4. The Relationship of the Autonomic Nervous System to General Medicine.
Thomas P. Sprunt,* Baltimore, Md.
5. The Internist as His Own Psychiatrist.
Alfred Stengel,† Philadelphia, Pa.
6. Experimental Uremia.
B. O. Raulston,* Los Angeles, Calif.
7. The Management of Edema.
Charles A. Elliott,* Chicago, Ill.
8. A Study of the Correlations between Physical Aspects of the Body and Disease Susceptibility.
Walter Freeman,* Washington, D.C.
9. The Treatment of Chronic Intractable Asthma with Pollen Extracts.
George L. Waldbott,* Detroit, Mich.

The Annual General Business Meeting of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports from the Executive Secretary and Treasurer will be read; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. George Morris Piersol, will be inducted into office.

Thursday Evening, 7:30 o'Clock

WINDSOR HALL

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Toastmaster: Charles F. Martin,† Montreal, Que., Dean, Faculty of Medicine, McGill University.

Address: "The Waste Spaces of Modern Education."

Dr. Stephen Leacock, Montreal, Que., William Dow Professor of Political Economy, McGill University.

FINAL GENERAL SESSION

Friday Afternoon, February 10, 1933

2:00 o'Clock

WINDSOR HALL

Presiding Officer

George Morris Piersol,* Philadelphia, Pa.

1. Evaluation of Various Types of Therapy in Chronic Arthritis Based on Results in One Thousand Cases.
W. Paul Holbrook,* Tucson, Ariz.
2. Research in Electrocardiography.
William Reid,* Boston, Mass.
3. A Standard Test for Measuring Blood Pressure Variability: Its Significance as an Index of Prehypertensive States.
George E. Brown,* Rochester, Minn.
4. Chronic Arterial Occlusion of the Extremities.
Duncan Graham, Toronto, Ont.
(Guest)
5. The Protean Nature of Subacute Bacterial Endocarditis.
John H. Musser,* New Orleans, La.

6. Clinical and Experimental Observations upon the Heart in Hyperthyroidism.
E. Cowles Andrus,* Baltimore, Md.
7. The Diagnosis and Medical Treatment of Angina Pectoris.
Paul D. White,* Boston, Mass.
8. Experimental and Clinical Studies on the Surgical Treatment of Angina Pectoris.
James C. White, Boston, Mass.
(Guest)
9. Pulsus Alternans.
John E. Greiwe,* Cincinnati, Ohio.
10. Aortic Stenosis, a Clinical and Pathological Consideration.
Louis F. Bishop, Jr.,* New York, N.Y.

SPECIAL CLINICS AND DEMONSTRATIONS

Clinics and demonstrations will be held in the forenoons from 9:00 to 12:00 daily, Tuesday to Friday, inclusive.

Tickets will be required for each and every one of the special clinics, ward rounds and demonstrations. The co-operation of everyone in securing his clinic tickets will assist greatly in distributing the attendance according to the capacity of each program. It is self-evident that a ward round arranged for twenty-five will lose its value for all if forty or fifty are present. Ticket registration naturally is the only effective method of keeping the attendance within the capacities indicated.

To all members of the College, registration blanks for the clinics and demonstrations are distributed with the official program. These registration blanks should be filled out and returned to the Executive Secretary at once. Reservations by mail cannot be made after January 20, but reservations may be made in person at the Registration Bureau on the evening preceding any clinic day. *Guests will kindly register for clinics at the Registration Bureau upon arrival at Montreal.*

A-I

Tuesday, February 7, 1933

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)

Medical Theatre

(Capacity—100)

- 9:00- 9:45 Metabolic Aspects of Progressive Muscular Dystrophy.
W. S. McCann, Rochester, N.Y.
- 9:45-10:30 Treatment of Complications in Diabetes Mellitus.
E. H. Mason.
- 10:30-11:15 X-Ray Examination of the Heart.
T. Homer Coffen, Portland, Ore.
- 11:15-12:00 Therapeutics of Acute Circulatory Failure.
G. R. Brow.

A-II

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)

Surgical Theatre

(Capacity—150)

- 9:00- 9:45 Peripheral Vascular Disease.
Mark Kaufmann.
- 9:45-10:30 Visceral Pain.
F. A. C. Scrimger.
- 10:30-11:15 Treatment of Pain in Buerger's Disease.
James C. White, Boston, Mass.
- 11:15-12:00 Lesions Due to Scalene Pressure and Their Treatment.
William V. Cone.

Tuesday, February 7, 1933 (Continued)

A-III

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Nurses' Theatre
(Capacity—250)

- 9:00- 9:45 Syphilitic Heart Disease.
John H. Musser, New Orleans, La.
9:45-10:30 Thoracic Aneurysm.
Reginald Fitz, Boston, Mass.
10:30-11:15 Pathogenesis of the Symptom Complex of Tabes.
C. K. Russel.
11:15-12:00 Treatment of Cardiovascular Syphilis.
E. Cowles Andrus, Baltimore, Md.

A-IV

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward B
(Capacity—15)

- 9:00- 9:45 Bedside Clinic: The Common Cold.
W. Blair Stewart, Atlantic City, N.J.
9:45-10:30 Bedside Clinic: Sinusitis and Asthma.
A. T. Henderson.
10:30-11:15 Bedside Clinic: Chronic Arthritides.
W. Paul Holbrook, Tucson, Ariz.
11:15-12:00 Bedside Clinic: Neurological Clinic.
Arthur W. Young.

A-V

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward D
(Capacity—50)

- 9:00-11:30 A selected group of interesting cases will be continuously demonstrated for all members who may be interested to examine them between these hours.

A-VI

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward K
(Capacity—15)

- 9:00-10:00 Bedside Clinic: Metabolism in Bone Diseases.
W. de M. Scriver.
10:00-11:00 Bedside Clinic: Myxoedema.
David P. Barr, St. Louis, Mo.

A-VII

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Medical Laboratories
(Capacity—15)

- 11:00-12:00 Studies in Biochemistry.
1. Fat Digestion and Absorption.
A. Krakower.

Tuesday, February 7, 1933 (Continued)

2. Blood Fats and Their Variations.
David Slight.
3. The Liver and Pancreas in Fat Metabolism.
Mrs. Venning.
4. Analytical Biochemical Methods.
R. U. Harwood.

B-I

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Surgical Theatre
(Capacity—200)

- 9:00- 9:45 Thoracic Pain.
C. A. Peters.
- 9:45-10:30 Bronchiectasis.
James Alex. Miller, New York, N.Y.
- 10:30-11:15 Pick's Disease.
Paul D. White, Boston, Mass.
- 11:15-12:00 Irradiation Treatment of Cancer about the Mouth.
George E. Pfahler, Philadelphia, Pa.

B-II

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Out-door Theatre
(Capacity—30)

- 9:00- 9:45 Cardiovascular Renal Syndrome.
G. C. Hale, London, Ont.
- 9:45-10:30 Asthma.
H. E. MacDermot.
- 10:30-11:15 Oxygen Therapy.
A. M. Burgess, Providence, R.I.
- 11:15-12:00 Stricture of Oesophagus.
R. E. Hodge.

B-III

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Pathological Theatre
(Capacity—60)

- 10:30-12:00 Pathological Conference.
J. E. Pritchard.

B-IV

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward A
(Capacity—50)

- 9:00-10:00 Ward Demonstration: Heart Disease in Pregnancy.
D. Grant Campbell.
- 10:00-11:00 Ward Demonstration: Placental Extracts in Gynecology.
A. D. Campbell.

Tuesday, February 7, 1933 (Continued)

B-V

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward C
(Capacity—50)

- 9:00-10:30 Ward Rounds.
A. H. Gordon.
10:30-12:00 Simultaneous Record of Heart Beat and Heart Sounds.
C. C. Birchard and Staff.

B-VI

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward E
(Capacity—50)

- 9:00-10:00 Ward Demonstration: Selected Cases of Skin Lesions.
F. J. Burgess.
10:00-11:00 Ward Demonstration: Essential Hypertension.
Joseph H. Barach, Pittsburgh, Pa.

C

McGILL UNIVERSITY MEDICAL SCHOOL
Biological Building
Department of Pharmacology, Fifth Floor
(Capacity—75)

- 9:00- 9:30 Moving Picture Film of Coronary Blood Flow.
R. L. Stehle.
9:30-10:00 Action of Pituitary Extract on Different Portions of the Gastro-intestinal Tract.
K. I. Melville.
10:00-10:30 Uric Acid Eliminants.
Hermann Schroeder.
10:30-10:45 Experimental Demonstration of the Effects of Coronary Constriction.
R. L. Stehle.
10:45-11:00 Chronic Mercury Poisoning.
K. I. Melville.
11:00-11:30 Moving Picture Film of Coronary Blood Flow.
R. L. Stehle.

D

McGILL UNIVERSITY MEDICAL SCHOOL
Pathological Institute
(3775 University St.)
Lecture Theatre
(Capacity—125)

- 9:00- 9:45 Bronchogenic Carcinoma (A Clinical, Bronchoscopic and Pathological Study).
L. H. Clerf and B. L. Crawford, Philadelphia, Pa.
9:45-10:30 Vegetal Foreign Bodies in the Bronchi.
D. H. Ballou.
10:30-11:15 Some Features in the Pathology of Coronary Disease of the Heart.
Oskar Klotz, Toronto, Ont.
11:15-12:00 Hemopoietic Effect of Nuclear Extractives Obtained from the Red Blood Cells of the Fowl.
Noble Wiley Jones, Portland, Ore.

Tuesday, February 7, 1933 (Continued)

E-I

NOTRE DAME HOSPITAL
(1560 Sherbrooke St., East)
Clinical Theatre
(Capacity—150)

- 9:00- 9:45 Title to be supplied later.
E. Rist, Paris, France.
9:45-10:30 Cardiac Insufficiency.
A. LeSage.
10:30-11:15 Electrocardiography in Cardiac Insufficiency.
A. de Guise.
11:15-12:00 Radiology in Cardiac Disease.
A. Laquerrière.

E-II

NOTRE DAME HOSPITAL.
(1560 Sherbrooke St., East)
Out-Door Department
(Capacity—50)

- 10:00-12:00 Demonstration of Cases in Dermatology and Syphilis.
Alberic Marin and Assistants.

E-III

NOTRE DAME HOSPITAL
(1560 Sherbrooke St., East)
Out-Door Department

- 10:00-12:00 Neurological Clinic.
Jean Saucier and Roma Amyot.

E-IV

NOTRE DAME HOSPITAL
(1560 Sherbrooke St., East)
Medical Wards
(Capacity—15)

- 10:00-12:00 Bedside Clinics.
E. P. Benoit and Assistants.

F-I

HOTEL DIEU
(65 Pine Avenue, West)
Clinical Theatre
(Capacity—150)

- 9:00- 9:45 Gastro-intestinal Clinic.
Frank Smithies, Chicago, Ill.
9:45-10:30 Treatment and Prevention of Congestive Cardiac Failure.
J. E. Dubé.
10:30-11:15 Collapse Therapy in Pulmonary Tuberculosis.
J. P. Dworetzky, Liberty, N.Y.
11:15-12:00 Spontaneous Pneumothorax.
Guy Hamel.

Tuesday, February 7, 1933 (Continued)

F-II

HOTEL DIEU
(65 Pine Avenue, West)
Medical Wards
(Capacity—15)

- 9:00-10:00 Bedside Clinic.
J. R. Pepin.
10:00-11:00 Bedside Clinic: Treatment of Peptic Ulcer.
Logan Clendening, Kansas City, Mo.
11:00-12:00 Bedside Clinic: Cardiac Clinic.
E. Tetreault.
-

G-I

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Medical Theatre
(Capacity—100)

- 9:00-10:00 Tuberculosis in Children.
Horton Casparis, Nashville, Tenn.
10:00-11:30 Clinical and Pathological Features of Rheumatic Fever in Children.
H. B. Cushing and L. J. Rhea.
11:30-12:00 An Estimate of the Value of Certain Observed Phenomena in Determining the
Activity of Rheumatic Infection.
R. R. Struthers.
-

G-II

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Baby Ward
(Capacity—15)

- 9:00-10:30 Ward Rounds.
Alton Goldbloom.
-

G-III

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Medical Ward
(Capacity—15)

- 10:30-12:00 Ward Rounds.
L. M. Lindsay.
-

H

HÔPITAL SAINTE JUSTINE
(6055 St. Denis St.)
No Program on Tuesday

I-I

McGILL UNIVERSITY MEDICAL SCHOOL
Medical Building
(3640 University St.)
Department of Anatomy, Third Floor
No Program on Tuesday

Tuesday, February 7, 1933 (Continued)

I-II

McGILL UNIVERSITY MEDICAL SCHOOL

Medical Building
(3640 University St.)
Osler Library, Third Floor
(Capacity—75)

- 9:30- 1:00 The Osler Library will be open between these hours, when Sir William Osler's collection may be inspected. A special exhibit of books famous in the history of Medicine and Science has been arranged.
- and
- 2:30- 5:00 The Librarian, Dr. W. W. Francis, will be present to receive all visitors.

I-III

McGILL UNIVERSITY MEDICAL SCHOOL

Medical Building
(3640 University St.)
Pathological Museum, Second Floor
(Capacity—75)

- Special exhibits will be set out consisting of:
- a) Collection on the Clinical Classification of Congenital Heart Disease recently presented at the Centenary Meeting of the British Medical Association:
 - b) Representative series from the Medical Historical Museum. These will include (1) Sir William Osler's Canadian Pathological collection, consisting of some 150 specimens, with its Bibliography; (2) other special exhibits illustrative of general Medical History.
- Maude E. Abbott.

Wednesday, February 8, 1933

A-I

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)
Medical Theatre
(Capacity—100)

- 9:00- 9:45 Heart Disease from the Obstetrician's Point of View.
John R. Fraser.
- 9:45-10:30 Handling of Heart Disease in Pregnancy.
S. Marx White, Minneapolis, Minn.
- 10:30-11:15 Factors Operative in Circulatory Failure.
Jonathan C. Meakins.
- 11:15-12:00 Some Aspects of the Etiology of Hematuria.
D. W. MacKenzie.

A-II

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)
Surgical Theatre
(Capacity—150)

- 9:00- 9:45 Physiology of Pulmonary Collapse.
Ronald V. Christie.
- 9:45-10:30 Results and Causes of Failure in Collapse Therapy.
Charles H. Cocke, Asheville, N.C.

Wednesday, February 8, 1933 (Continued)

- 10:30-11:15 Indications for Surgical Interference in Pulmonary Tuberculosis.
Lawrason Brown, Saranac Lake, N.Y.
- 11:15-12:00 Results of Surgical Treatment of Pulmonary Tuberculosis.
E. W. Archibald.
-

A-III

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Nurses' Theatre
(Capacity—250)

- 9:00-10:00 Neurogenic Factors in Epilepsy.
Stanley Cobb, Boston, Mass.
- 10:00-11:00 A Discussion of the Etiology and Treatment of Epilepsy.
Henry Rawle Geyelin, New York, N.Y.
- 11:00-12:00 Focal Epilepsy—Its Diagnosis and Treatment.
Wilder Penfield.
-

A-IV

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward B
(Capacity—15)

- 9:00- 9:45 Bedside Clinic: Blood Transfusion (A Demonstration)
Henry F. Stoll, Hartford, Conn.
- 9:45-10:30 Bedside Clinic.
W. F. Hamilton.
- 10:30-11:15 Bedside Clinic: Acute Pulmonary Tuberculosis.
J. R. Byers.
- 11:15-12:00 Bedside Clinic: Gastro-intestinal Clinic.
C. J. Tidmarsh.
-

A-V

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward D
(Capacity—50)

- 9:00-11:30 Demonstration of Dermatological Cases.
Philip Burnett.
-

A-VI

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward K
(Capacity—15)

- 9:00-10:00 Bedside Clinic: Atypical Renal Glycosuria.
E. H. Mason.
- 10:00-11:00 Bedside Clinic: Diabetes.
Joseph H. Barach, Pittsburgh, Pa.

Wednesday, February 8, 1933 (Continued)

A-VII

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)

Medical Laboratories

(Capacity—15)

- 11:00-12:00 Demonstrations in Cardiac Physiology:
1. The Continuous Registration of the Heart and Respiratory Rate in Man.
Ronald V. Christie and G. H. Shepherd.
 2. Studies of the Electrocardiographic "T" Wave.
G. R. Brow and D. V. Holman.
 3. Animal Studies of Acute Heart Failure.
Gerald Evans.
 4. Visualization of Liver and Spleen by X-Ray with Thorium Dioxide.
R. Gottlieb.
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B-I

MONTREAL GENERAL HOSPITAL

(66 Dorchester St., East)

Surgical Theatre

(Capacity—200)

- 9:00- 9:45 Liver Function and Laboratory Tests in Biliary Disease.
T. B. Magath, Rochester, Minn.
- 9:45-10:30 X-Ray versus Clinical Diagnosis in Biliary Disease.
W. L. Ritchie.
- 10:30-11:15 The Management of Hepatic Disease.
Charles A. Elliott, Chicago, Ill.
- 11:15-12:00 Surgical Aspects of Diseases of the Biliary Passages.
A. T. Bazin.
-

B-II

MONTREAL GENERAL HOSPITAL

(66 Dorchester St., East)

Out-Door Theatre

(Capacity—30)

- 9:00- 9:45 Cardiac Clinic.
Wm. D. Reid, Boston, Mass.
- 9:45-10:30 Renal Glycosuria with Acidosis.
A. F. Fowler.
- 10:30-11:15 Splenomegaly.
E. H. Falconer, San Francisco, Calif.
- 11:15-12:00 Problems in Hematology.
E. S. Mills.
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B-III

MONTREAL GENERAL HOSPITAL

(66 Dorchester St., East)

Pathological Theatre

(Capacity—60)

- 10:30-12:00 Pathological Conference.
L. J. Rhea.
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B-IV

MONTREAL GENERAL HOSPITAL

(66 Dorchester St., East)

Ward A

No program on Wednesday.

Program of the Montreal Meeting

Wednesday, February 8, 1933 (Continued)

B-V

MONTREAL GENERAL HOSPITAL
(65 Dorchester St., East)
Ward C
(Capacity—50)

10:30-12:00 Simultaneous Record of Heart Beat and Heart Sounds.
C. C. Birchard and Staff.

B-VI

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward E
(Capacity—50)

9:00-10:00 Ward Demonstration: Lead Poisoning.
Maurice C. Pincoffs, Baltimore, Md.
10:00-11:00 Ward Demonstration: Neurological Clinic.
F. H. MacKay.

C

McGILL UNIVERSITY MEDICAL SCHOOL
Biological Building
Department of Physiology, Fourth Floor
(Capacity—75)

9:00- 9:15 Experiments on the Labyrinth in Relation to Posture.
W. J. McNally and John Tait.
9:15- 9:45 Experiments on Hearing in Conditioned Cats and Dogs.
S. Dworkin and G. F. Sutherland.
9:45-10:00 Experiments on Tremor Sense in Conditioned Cats.
S. Dworkin.
10:00-10:15 Electrical Records from the Eighth Nerve.
D. A. Ross.
10:15-10:30 Mechanism of Natural Arrest of Hemorrhage from a Wound.
John Tait.
10:30-12:00 Experiments to Demonstrate the Modern Conceptions of Gastric Secretion and
Their Bearing on Gastric Digestion.
B. P. Babkin and Assistants.

D

McGILL UNIVERSITY MEDICAL SCHOOL
Pathological Institute
(3775 University St.)
Lecture Theatre
(Capacity—125)

9:00- 9:40 The Heart Beat and Electrocardiograph (Moving Picture).
L. M. Hurxthal, Boston, Mass.
9:45-10:00 Syndrome of the Superior Cerebellar Artery (Moving Picture).
C. K. Russel.
10:00-10:45 Chronic Arthritis (Moving Picture).
W. Paul Holbrook, Tucson, Ariz.

E-I

NOTRE DAME HOSPITAL
(1560 Sherbrooke St., East)
Clinical Theatre
(Capacity—150)

9:00- 9:45 Pathological Anatomy of Chronic Gastritis.
Pierre Masson.

Wednesday, February 8, 1933 (Continued)

- 9:45-10:30 Symptomatology of Peptic Ulcer.
E. P. Benoit.
- 10:30-11:15 The Radiological Diagnosis of Peptic Ulcer.
A. Laquerrière.
- 11:15-12:00 The Treatment of Peptic Ulcer.
H. Gélinas.

E-II

NOTRE DAME HOSPITAL
(1560 Sherbrooke St., East)
Out-Door Department
No Program on Wednesday

E-III

NOTRE DAME HOSPITAL
(1560 Sherbrooke St., East)
Out-Door Department
(Capacity—10)

- 10:00-12:00 Neurological Clinic.
Edgar Langlois and Assistants.

E-IV

NOTRE DAME HOSPITAL
(1560 Sherbrooke St., East)
Medical Wards
(Capacity—15)

- 10:00-12:00 Bedside Clinics.
A. LeSage and Assistants.

F-I

HOTEL DIEU
(65 Pine Avenue, West)
Clinical Theatre
(Capacity—150)

- 9:00- 9:45 Title to be supplied later.
E. Rist, Paris, France.
- 9:45-10:30 General Survey of Pyelitis.
Oscar Mercier.
- 10:30-11:15 Duodenal Ulcer.
Lay Martin, Baltimore, Md.
- 11:15-12:00 X-Ray Demonstration.
Leo Pariseau.

F-II

HOTEL DIEU
(65 Pine Avenue, West)
No Program on Wednesday

G-I

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Medical Theatre
(Capacity—100)

- 9:00-10:00 1. Coeliac Disease.
2. Bronchiectasis and Asthma.
Alan Brown, Toronto, Ont.

Wednesday, February 8, 1933 (Continued)

- 10:00-10:30 Relation of Sinus Infection to Respiratory Diseases in Infancy and Childhood.
A. B. Chandler.
- 10:30-11:15 Renal Dwarfism.
L. M. Lindsay.
- 11:15-12:00 A Case of Osteomalacia with Cloudiness of the Cornea.
S. Graham Ross.
-

G-II

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Baby Ward
(Capacity—15)

- 9:00-10:30 Ward Rounds.
H. P. Wright.
-

G-III

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Medical Ward
(Capacity—15)

- 10:30-12:00 Ward Rounds.
H. B. Cushing.
-

H

HOPITAL SAINTE JUSTINE
(6055 St. Denis St.)
Clinical Theatre
(Capacity—100)

- 9:00- 9:45 Asthma in Children.
Horton Casparis, Nashville, Tenn.
- 9:45-10:30 Les état de dénutrition du nourrisson. (The State of Undernourishment in Infants).
Gaston Lapierre.
- 10:30-11:15 Le problème de l'épilepsie infantile. (The Problem of Infantile Epilepsy.)
J. A. Lussier.
- 11:15-12:00 Le tétanie infantile. (Infantile Tetany.)
Henri Baril.
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I-I

McGILL UNIVERSITY MEDICAL SCHOOL
Medical Building
(3640 University St.)
Department of Anatomy, Third Floor
No Program on Wednesday.

I-II

McGILL UNIVERSITY MEDICAL SCHOOL
Medical Building
(3640 University St.)
Osler Library, Third Floor
(Capacity—75)

- 9:30- 1:00 The Osler Library will be open between these hours, when Sir William Osler's
and collection may be inspected. A special exhibit of books famous in the
history of Medicine and Science has been arranged.

- 2:30- 5:00 The Librarian, Dr. W. W. Francis, will be present to receive all visitors.

Wednesday, February 8, 1933 (Continued)

I-III

McGILL UNIVERSITY MEDICAL SCHOOL

Medical Building
(3640 University St.)
Pathological Museum, Second Floor
(Capacity—75)

Special Exhibits will be set out consisting of:

- a) Collection on the Clinical Classification of Congenital Heart Disease recently presented at the Centenary Meeting of the British Medical Association;
- b) Representative series from the Medical Historical Museum. These will include (1) Sir William Osler's Canadian Pathological collection, consisting of some 150 specimens, with its Bibliography; (2) Other special exhibits illustrative of general Medical History.
Maude E. Abbott.

Thursday, February 9, 1933

A-I

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)
Medical Theatre
(Capacity—100)

- 9:00- 9:45 Types of Chronic Rheumatism.
Ralph Kinsella, St. Louis, Mo.
- 9:45-10:30 Intravenous Vaccine Therapy in Chronic Arthritis.
W. B. Rawls, New York, N.Y.
- 10:30-11:15 Chronic Intractable Asthma.
G. L. Waldbott, Detroit, Mich.
- 11:15-12:00 Diagnostic Clinic.
Logan Clendening, Kansas City, Mo.

A-II

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)
Surgical Theatre
(Capacity—150)

- 9:00- 9:45 Hypertension and Cerebral Phenomena.
Alfred Gordon, Philadelphia, Pa.
- 9:45-10:30 Angina Pectoris.
J. B. Wolffe, Philadelphia, Pa.
- 10:30-11:15 Jaundice in Cardiac Disease.
Alfred Stengel, Philadelphia, Pa.
- 11:15-12:00 Diuretics.
D. Sclater Lewis.

A-III

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)
Nurses' Theatre
(Capacity—250)

- 9:00- 9:45 The Relation of Emotional Factors to Thyroid Disorders.
James H. Means, Boston, Mass.

Thursday, February 9, 1933 (Continued)

- 9:45-10:30 The Importance of Mental Aspects in the Etiology and Treatment of Tuberculosis.
Lawrason Brown, Saranac Lake, N.Y.
- 10:30-11:15 The Psychiatric Factors in the Causation of Gastro-intestinal Disorders.
W. C. Alvarez, Rochester, Minn.
- 11:15-12:00 Emotional Factors in Organic Disease.
Franz Alexander, Chicago, Ill.
-

A-IV

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)

Ward B

(Capacity—50)

- 9:00-11:30 A selected group of interesting cases will be continuously demonstrated for all members who may be interested to examine them between these hours.
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A-V

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)

Ward D

(Capacity—15)

- 9:00- 9:45 Bedside Clinic: Chronic Chlorosis.
William B. Castle, Boston, Mass.
- 9:45-10:30 Bedside Clinic.
C. F. Moffatt.
- 10:30-11:15 Bedside Clinic: Clinical Diagnosis of Cardio-arrhythmias.
Wm. D. Reid, Boston, Mass.
- 11:15-12:00 Bedside Clinic: Peptic Ulcer.
C. G. Sutherland.
-

A-VI

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)

Ward K

(Capacity—15)

- 9:00-10:00 Bedside Clinic: Obesity.
James S. McLester, Birmingham, Ala.
- 10:00-11:00 Bedside Clinic: Toxic Adenoma of the Thyroid.
Henry M. Thomas, Jr., Baltimore, Md.
-

A-VII

ROYAL VICTORIA HOSPITAL

(Pine Avenue, West)

Medical Laboratories

(Capacity—15)

- 11:00-12:00 Demonstrations in Respiratory Physiology:
1. The Measurement of Lung Volume without Forced Breathing.
Ronald V. Christie and C. A. McIntosh.
 2. Variations in Lung Volume and its Functional Significance in Disease.
 - (a) Normals,
 - (b) Emphysema,
 - (c) Pneumothorax, Phrenicotomy and Thoracoplasty,
 - (d) Lungectomy,
 - (e) Respiratory Neurosis.
 Ronald V. Christie and C. A. McIntosh.

Thursday, February 9, 1933 (Continued)

B-I

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Surgical Theatre
(Capacity—200)

- 9:00- 9:45 Diabetes.
E. P. Joslin, Boston, Mass.
9:45-10:30 Tuberculosis and Diabetes.
W. R. Kennedy.
10:30-11:15 The Fundas Oculi in Diabetes Mellitus.
S. H. McKee.
11:15-12:00 The Treatment of Diabetes.
Henry Rawle Geyelin, New York, N.Y.
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B-II

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Out-Door Theatre
(Capacity—30)

- 9:00- 9:45 Poliomyelitis.
P. N. MacDermot.
9:45-10:30 Encephalitis.
Lorne C. Montgomery.
10:30-11:15 Virus Diseases.
O. H. Perry Pepper, Philadelphia, Pa.
11:15-12:00 A Discussion of the Use of Vaccine in Chronic Arthritis.
Sydney R. Miller, Baltimore, Md.
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B-III

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Pathological Theatre
(Capacity—60)

- 10:30-12:00 Pathological Conference: Malignancy and Infection of the Genito-urinary Tract.
F. S. Patch.
-

B-IV

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward A
No Program on Thursday.

B-V

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward C
(Capacity—50)

- 9:00-10:00 Circulatory Disturbances of the Extremities.
George E. Brown, Rochester, Minn.
10:00-11:00 Thrombo-angiitis Obliterans.
Thomas P. Sprunt, Baltimore, Md.
11:00-12:00 Demonstration of Tests for Vascular Disease of Extremities.
C. W. Fullerton.

Program of the Montreal Meeting

Thursday, February 9, 1933 (Continued)

5. *Chemistry of Lead Poisoning*: I. M. Rabinowitch.
Methods of detection of lead in the body. Explanation of deposition of lead in the body and its removal.
6. *Treatment*: S. Graham Ross.
Dietary and medicinal methods of fixation of lead in body and deleading.
Methods for relief of symptoms.

G-II

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Baby Ward
(Capacity—15)

9:00-10:30 Ward Rounds.
Alan Brown, Toronto, Ont.

G-III

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Medical Ward
(Capacity—15)

10:30-12:00 Ward Rounds.
A. B. Chandler.

H

HOPITAL SAINTE JUSTINE
(6055 St. Denis St.)
Clinical Theatre
No Program on Thursday.

I-I

McGILL UNIVERSITY MEDICAL SCHOOL
Medical Building
(3640 University St.)
Department of Anatomy, Third Floor
No Program on Thursday.

I-II

McGILL UNIVERSITY MEDICAL SCHOOL
Medical Building
(3640 University St.)
Osler Library, Third Floor
(Capacity—75)

9:30- 1:00 The Osler Library will be open between these hours, when Sir William Osler's
and collection may be inspected. A special exhibit of books famous in the
history of Medicine and Science has been arranged.
2:30- 5:00 The Librarian, Dr. W. W. Francis, will be present to receive all visitors.

I-III

McGILL UNIVERSITY MEDICAL SCHOOL
Medical Building
(3640 University St.)
Pathological Museum, Second Floor
(Capacity—75)
Special Exhibits will be set out consisting of:

Thursday, February 9, 1933 (Continued)

- a) Collection on the Clinical Classification of Congenital Heart Disease recently presented at the Centenary Meeting of the British Medical Association;
- b) Representative series from the Medical Historical Museum. These will include (1) Sir William Osler's Canadian Pathological collection, consisting of some 150 specimens, with its Bibliography; (2) Other special exhibits illustrative of general Medical History.

Maude E. Abbott.

Friday, February 10, 1933

A-I

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Medical Theatre
(Capacity—100)

- 9:00- 9:45 Diverticulitis.
R. H. M. Hardisty.
- 9:45-10:30 X-Ray Diagnosis of Diverticula of the Gastro-intestinal Tract.
E. C. Brooks.
- 10:30-11:15 Progress in the Management of Various Types of Colitis.
J. A. Bagen, Rochester, Minn.
- 11:15-12:00 Jaundice in Diagnosis.
Lay Martin, Baltimore, Md.

A-II

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Surgical Theatre
(Capacity—150)

- 9:00- 9:45 Erythema Nodosum and Tuberculosis.
H. B. Cushing.
- 9:45-10:30 Pulmonary Neoplasms.
Harlow Brooks, New York, N.Y.
- 10:30-11:15 Differential Diagnosis of Congenital Heart Disease, with Illustrative Cases.
Maude E. Abbott.
- 11:15-12:00 X-Ray Diagnosis of Bone Lesions.
A. Howard Pirie.

A-III

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Nurses' Theatre
(Capacity—250)

- 9:00- 9:45 Pernicious Anemia.
Cyrus C. Sturgis, Ann Arbor, Mich.
- 9:45-10:30 Neutropenia.
J. Kaufmann.
- 10:30-11:15 Monocytic Leukemia.
Thomas P. Sprunt, Baltimore, Md.
- 11:15-12:00 Myelotoxic Anemia.
R. Gottlieb.

Friday, February 10, 1933 (Continued)

A-IV

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward B
(Capacity—50)

9:00-11:30 A selected group of interesting cases will be continuously demonstrated for all members who may be interested to examine them between these hours.

A-V

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward D
(Capacity—15)

9:00- 9:45 Bedside Clinic.
W. F. Hamilton.
9:45-10:30 Bedside Clinic: Cardiac Asthma.
Maurice C. Pincoffs, Baltimore, Md.
10:30-11:15 Bedside Clinic: Diagnostic Clinic on Hepatic Enlargement.
Duncan Graham, Toronto, Ont.
11:15-12:00 Bedside Clinic.
D. Sclater Lewis.

A-VI

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Ward K
(Capacity—15)

9:00-10:00 Bedside Clinic: Tetany.
David P. Barr, St. Louis, Mo.
10:00-11:00 Bedside Clinic: The Diabetic Child.
E. H. Mason.

A-VII

ROYAL VICTORIA HOSPITAL
(Pine Avenue, West)
Neuro-pathological Laboratories
(Capacity—15)

11:00-12:00 Demonstration of Neuro-pathological Material.
W. V. Conc, Lyle Gage and Assistants.

B-I

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Surgical Theatre
(Capacity—200)

9:00- 9:45 Clinical Aspects of Hyperthyroidism.
Roger I. Lee, Boston, Mass.
9:45-10:30 Pitfalls in Interpretation of Tests for Basal Metabolism.
I. M. Rabinowitch.
10:30-11:15 The Present Status of the Medical Treatment of Hyperthyroidism.
James H. Means, Boston, Mass.
11:15-12:00 Surgical Aspects of Hyperthyroidism.
E. M. Eberts.

B-II

Friday, February 10, 1933 (Continued)

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Out-Door Theatre
(Capacity—30)

- 9:00- 9:45 Arteriosclerotic Heart Disease.
F. M. Smith, Iowa City, Iowa.
9:45-10:30 Aortic Valvular Disease.
L. F. Bishop, Jr., New York, N.Y.
10:30-11:15 Digitalis Therapy.
H. N. Segall.
11:15-12:00 Quinidine Therapy.
Neil Feeney.
-

B-III

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Pathological Theatre
(Capacity—60)

- 10:30-12:00 Pathological Conference.
L. J. Rhea.
-

B-IV

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward A
No Program on Friday.

B-V

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward C
(Capacity—50)

- 9:00-10:00 Ward Demonstration: Silicosis.
J. G. Browne.
10:00-11:00 Ward Demonstration: Delayed Development of Pneumoconiosis.
P. H. Pierson, San Francisco, Calif.
11:00-12:00 Ward Demonstration: Pneumothorax.
J. B. Ross.
-

B-VI

MONTREAL GENERAL HOSPITAL
(66 Dorchester St., East)
Ward E
(Capacity—50)

- 9:00-10:30 Ward Rounds.
C. P. Howard.
-

C

McGILL UNIVERSITY MEDICAL SCHOOL
Biological Building
No Program on Friday.

Friday, February 10, 1933 (Continued)

D

McGILL UNIVERSITY MEDICAL SCHOOL
 Pathological Institute
 (3775 University St.)
 Lecture Theatre
 (Capacity—125)

- 9:00-10:00 The Clinical Significance of Diphtheroid Bacilli; A Critical Analysis of 510
 Positive Blood Cultures from 320 Patients.
 R. H. Durham, Detroit, Mich.
- 10:00-11:00 A New Conception of the Pathology of Experimental Tuberculosis.
 S. A. Petroff, Saranac Lake, N.Y.
- 11:00-12:00 Renal Cortical Necrosis.
 W. de M. Sriver.

E-I

NOTRE DAME HOSPITAL
 (1560 Sherbrooke St., East)
 Clinical Theatre
 (Capacity—150)

- 9:00- 9:45 Lipoidic Nephrosis.
 A. Leger.
- 9:45-10:30 Cholecystitis.
 J. Albert Rouleau.
- 10:30-11:15 Cholecystography.
 J. A. Mousseau.
- 11:15-12:00 Cholelithiasis.
 Frank Smithies, Chicago, Ill.

E-II

NOTRE DAME HOSPITAL
 (1560 Sherbrooke St., East)
 Out-Door Department
 (Capacity—50)

- 10:00-12:00 Demonstration of Cases in Dermatology and Syphilis.
 Alberic Marin and Assistants.

E-III

NOTRE DAME HOSPITAL
 (1560 Sherbrooke St., East)
 Out-door Department
 No Program on Friday.

E-IV

NOTRE DAME HOSPITAL
 (1560 Sherbrooke St., East)
 Medical Wards
 (Capacity—15)

- 10:00-12:00 Bedside Clinics.
 A. LeSage and Assistants.

Friday, February 10, 1933 (Continued)

F-I

HOTEL DIEU
(65 Pine Avenue, West)
Clinical Theatre
(Capacity—150)

- 9:00- 9:45 Title to be supplied later.
E. Rist, Paris, France.
9:45-10:30 External Causes of Ocular Muscle Deficiency.
P. E. Bousquet.
10:30-11:15 Cardiac Clinic.
Walter L. Bierring, Des Moines, Iowa.
11:15-12:00 Goitre.
Donald Hingston.
-

F-II

HOTEL DIEU
(65 Pine Avenue, West)
No Program on Friday.

G-I

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Medical Theatre
(Capacity—100)

- 9:00- 9:30 Diphtheria Immunization by Intracutaneous Methods.
Alton Goldbloom.
9:30-10:00 Simple Anemias of Infancy.
H. P. Wright.
10:00-10:30 Treatment of Congenital Lues.
A. K. Geddes.
10:30-11:00 Demonstration of Unusual Skin Diseases Encountered in Children.
L. P. Ereaux.
11:00-12:00 Demonstration of Neurological Cases.
A. W. Young.
-

G-II

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Baby Ward
(Capacity—15)

- 9:00-10:30 Ward Rounds.
R. R. Struthers.
-

G-III

CHILDREN'S MEMORIAL HOSPITAL
(1415 Cedar Avenue)
Medical Ward
(Capacity—15)

- 10:30-12:00 Ward Rounds.
S. Graham Ross.

Friday, February 10, 1933 (Continued)

H

HÔPITAL SAINTE JUSTINE

(6055 St. Denis St.)

Clinical Theatre

(Capacity—100)

- 9:00- 9:45 Broncho-pneumonies à Plasmode. (Malarial Broncho-pneumonia.)
Pierre Masson.
- 9:45-10:30 Le Vaccin B. C. G. (Vaccine B. C. G.).
J. A. Beaudouin.
- 10:30-11:15 Diagnostic des Cardiopathies Infantiles. (Diagnosis of Cardiopathies in Infants.)
Paul Letondal.
- 11:15-12:00 Le Diabète Infantile. (Infantile Diabetes.)
A. Dutilly.

I-I

MCGILL UNIVERSITY MEDICAL SCHOOL

Medical Building

(3640 University St.)

Department of Anatomy, Third Floor

(Capacity—100)

- 9:00-10:00 Consideration of Referred Pain.
S. E. Whitnall.
- 10:00-11:00 The Neurogenic Factor in Gastric and Duodenal Ulcer.
J. Beattie.
- 11:00-12:00 The Demonstration of Preparations of the Nasal Accessory Sinuses.
H. E. MacDermot.

I-II

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Medical Building

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Osler Library, Third Floor

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Maude E. Abbott.

OBITUARIES

DOCTOR ALFRED LEFTWICH
GRAY

Dr. Alfred Leftwich Gray (Fellow), died at his home in Richmond, Va., October 13, 1932, after an illness of eighteen months.

Dr. Gray was born October 2, 1873, at Palmyra, Va., and received his academic and medical training at the University of Virginia, from which he was graduated in 1897. In 1899 he joined the faculty of the University College of Medicine, where he served as Professor of Physiology from 1901 until that school was merged with the Medical College of Virginia in 1913. He was a pioneer in Roentgenology and in 1916 became Professor of Roentgenology in the Medical College of Virginia, a position he continued to fill until his death. In addition to teaching and private practice he was Roentgenologist to the Hospital Division of the Medical College of Virginia, St. Luke's Hospital and Pine Camp Hospital, and was Dean of the Medical College of Virginia from 1913 to 1919.

At the beginning of the World War Dr. Gray was commissioned Major in the Medical Reserve Corps and, as commanding officer, organized and conducted the Richmond School of Military Roentgenologists. He was an active member of numerous medical organizations and served as president of the Richmond Academy of Medicine, Medical Society of Virginia, American College of Roentgenology and American Roentgen Ray Society. He had been a Fellow of the Ameri-

can College of Physicians since 1920. While a recital of the posts he held indicates a life of accomplishment far beyond the ordinary, it fails to portray fully those qualities of mind and heart that will linger longest in the memories of those who knew him. To few, indeed, is it given to attain the degree of confidence and affection in which Dr. Gray was held by his fellow physicians. His ability, energy and sense of fairness marked him as a leader and he was chosen often to represent the various professional and educational organizations with which he was connected. Especially in times of stress, when men lose their heads and passion rules, his innate tact and sound judgment shone brilliantly. Of his time and talents he gave generously. To the hundreds of physicians and students with whom he labored he was ever the sympathetic friend and genial companion, who was always accessible and always willing to help.

In the passing of Dr. Gray the State has lost one of its most useful sons; the medical profession a most loyal and devoted member; and his associates a wise counsellor and faithful friend.

(Furnished by J. MORRISON HUTCHINSON, M.D., F.A.C.P., Governor for Virginia)

DOCTOR EDWARD BATES
BLOCK

Dr. Edward Bates Block (Fellow). Atlanta, Ga., died October 25, 1932; aged, fifty-eight years.

Dr. Block received his medical de-

College News Notes

gree from the University of Virginia Department of Medicine in 1895. Thereafter he was Assistant Resident Physician at Johns Hopkins Hospital from 1895 to 1897; Assistant Pathologist and Bacteriologist, University of Minnesota, 1897 to 1898; Assistant in Neurology at the University of Strassburg from 1898 to 1899; Volunteer Assistant, University of Prague, 1899 to 1900; Assistant Neurologist, Johns Hopkins Hospital, 1900 to 1901; Professor of Neurology and Psychiatry, Emory University School of Medicine, 1901 to the date of his death. He was also Visiting Neurologist to the Grady Memorial Hospital and Visiting Neurologist and Psychiatrist to the Wesley Memorial Hospital, both of Atlanta.

Dr. Block was the author of a large number of publications. He was an ex-President of the Fulton County (Ga.) Medical Society, ex-President of the Atlanta Neurological Association, a member of the Medical Association of Georgia, a member of the Southern Interurban Clinical Club, a member of the Southern Medical Association, a member of the American Neurological Association, a member of the Association for Research in Nervous and Mental Diseases, a member of the American Medical Association, a Fellow of the American Association for Advancement of Science, and had been a Fellow of the American College of Physicians since 1928.

ANNALS OF INTERNAL MEDICINE

VOLUME VI

FEBRUARY, 1933

NUMBER 8

The Anatomy of the Autonomic Nervous System With Special Reference to the Innervation of the Skeletal Muscles and Blood Vessels*

By S. W. RANSON, M.D., *Chicago, Illinois*

IT will avoid confusion if at the beginning of this symposium we recognize that the sympathetic nervous system as defined in descriptive anatomy is not exactly what the physiologist has in mind when he uses this much abused term. The anatomist thinks of the system as he sees it in the dissecting room, and we shall begin with this simple approach and later define the term in the more restricted sense in which Dr. Cannon will probably use it.

The sympathetic nervous system, in the anatomical sense, is an aggregation of ganglia, nerves, and plexuses through which the viscera, glands, heart, blood vessels, and smooth muscle in other situations receive their innervation. The most conspicuous feature of the system is a pair of ganglionated nerve cords, or sympathetic trunks, which extend vertically through the neck, thorax, and abdomen. Each sympathetic trunk is composed of a series of ganglia bound together by short nerve strands. Every spinal nerve is connected with the sympathetic trunk of its own side by one or more gray rami communicantes through which it receives sympathetic fibers for the control of blood vessels, sweat glands, and smooth muscles of the hair follicles (Figure 1). The majority of the nerve fibers taking origin in the ganglia of the sympathetic chain are distributed through the gray rami and the spinal nerves. The ganglia of the thoracic and abdominal portions of the chain are less concerned with visceral activity than with constriction of the peripheral blood vessels, erection of the hairs, and secretory activity of the sweat glands. But the cervical ganglia bear an intimate relation to the viscera of the head, neck, and thorax.

The thoracic and the upper lumbar nerves are connected with the sympathetic chain by white as well as gray rami communicantes. These white rami contain visceral efferent fibers

*Read before the American College of Physicians, San Francisco, California, April 8, 1932.

which take origin from cells in the gray matter of the spinal cord, travel through the ventral roots and white rami, and enter the sympathetic system, to terminate in synaptic relation with the nerve cells found in the sympathetic ganglia. These fibers are often designated as preganglionic fibers, while those that arise in the ganglia and relay the impulses onward are called postganglionic. The gray rami contain postganglionic fibers most of which have no myelin sheaths; the

of descending fibers from the white rami of the lower thoracic and upper lumbar spinal nerves.

Those fibers of the white rami, which are concerned with the innervation of the abdominal viscera, pass into the splanchnic nerves and end in the celiac ganglion. These fibers reach the splanchnic nerves after passing through the lower half of the thoracic sympathetic chain; but they are not interrupted in the chain ganglia through which they pass.

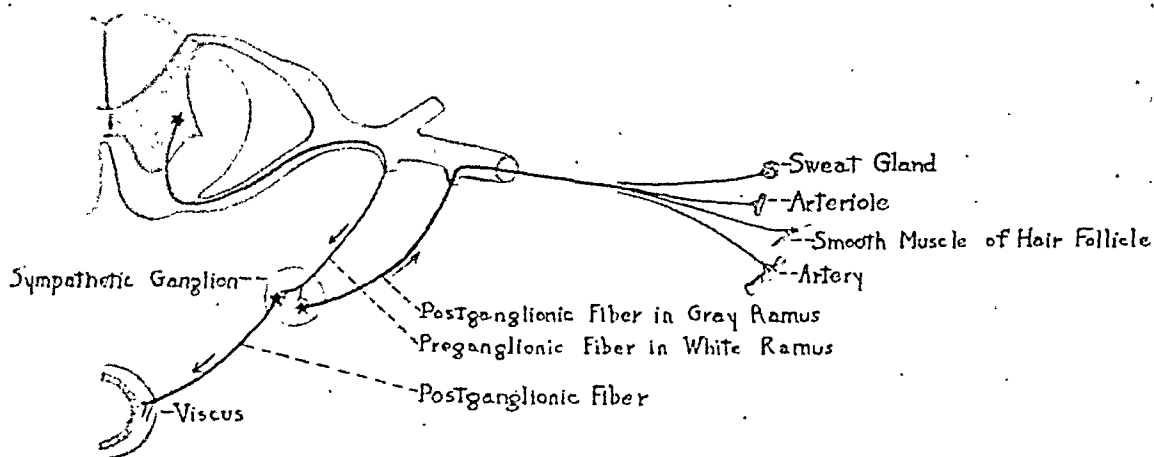


FIG. 1. Diagram of pre- and postganglionic nerve fibers.

white rami contain preganglionic fibers, which are all of small caliber and myelinated.

The majority of the preganglionic fibers turn either upward or downward in the sympathetic chain, and run for varying distances within it before ending in its ganglia. The cervical sympathetic trunk is composed almost exclusively of preganglionic efferent fibers, derived through the white rami from the upper thoracic nerves and ascending to terminate in the cervical sympathetic ganglia. The lumbar and sacral portions of the trunk are composed in the major part

The sympathetic nervous system, as defined anatomically, receives additional fibers from the spinal cord by way of the visceral branches of the third and fourth sacral nerves. These make no connection with the sympathetic chain but join with the hypogastric nerves to form the vesical plexus, which is situated lateral to the neck of the bladder and from which fibers are distributed to the pelvic viscera.

The peripheral sympathetic plexuses are joined by fibers from certain of the cranial nerves. Of these the vagus makes the largest contribution. It

gives off several cardiac branches. The superior cardiac branch of the left vagus runs in front of the arch of the aorta and enters the superficial part of the cardiac plexus. The other cardiac branches from the left vagus and all from the right vagus enter the deep part of the cardiac plexus which is situated behind the aortic arch. In these plexuses the vagal fibers are joined by others from the cervical sympathetic ganglia and are distributed along with these sympathetic fibers through the plexuses accompanying the coronary arteries.

Each vagus gives off two or three small branches, which join the anterior pulmonary plexus in front of the root of the lung, and then pass behind the bronchus, giving off numerous branches which are joined by filaments from the thoracic sympathetic chain to form the posterior pulmonary plexus. Below the root of the lung the two vagi break up into branches which form a plexus surrounding the esophagus. Fibers from the left vagus supply the anterior surface of the stomach and some run through the hepatic branch to the left lobe of the liver. Fibers from the right vagus are distributed to the posterior surface of the stomach, and to the celiac plexus. Through the celiac plexus fibers from the right vagus reach the liver, gall-bladder, pancreas, spleen, kidneys, suprarenal glands, and intestines.

There are then three streams of preganglionic visceral efferent fibers: (1) a cranial stream from the third, seventh, ninth, and tenth cranial nerves; (2) a thoracolumbar stream from the thoracic and upper lumbar spinal nerves by way of the white

rami; and (3) a sacral stream from the second, third, and fourth sacral nerves. The cervical and lower lumbar nerves contain no visceral efferent fibers and thus serve to separate the three streams.

These three groups of preganglionic visceral efferent fibers, and the postganglionic neurones which are associated with them, constitute what is known as the autonomic nervous system. In other words, this term is used to designate the aggregate of all visceral efferent neurones, both pre- and postganglionic, irrespective of whether they are associated with cerebral or spinal nerves. It is through this system that the glands, heart, and smooth muscle receive their efferent innervation. Two principal divisions of the autonomic system are recognized, namely thoracolumbar and craniosacral. These divisions are also known as the sympathetic and parasympathetic systems. Now we are using the term sympathetic system in its restricted physiological sense, not for something which can be isolated in the dissecting room, but to designate a particular group of visceral efferent neurones.

The preganglionic fibers of the thoracolumbar or sympathetic division leave the cord by way of the thoracic and upper lumbar spinal nerves, run by way of the white rami to the sympathetic chain and end either in the ganglia of this chain or in the prevertebral ganglia. The preganglionic fibers of the craniosacral or parasympathetic division do not join the sympathetic chain but end in terminal ganglia situated either in or close to the organ supplied. In their

failure to make connections with the sympathetic chain, and in their relation to the terminal ganglia, the fibers of the cranial and sacral streams agree with each other and differ from those of the thoracolumbar outflow. Also in their response to drugs like atropin and adrenalin the two former agree with each other and differ from the latter. There are, therefore, good reasons for grouping the cranial and sacral divisions of the autonomic system together under the designation of the parasympathetic system.

The rami communicantes, sympathetic chain, and splanchnic nerves contain no parasympathetic fibers; but in most of the peripheral plexuses sympathetic and parasympathetic fibers are intermingled. In this way the viscera receive fibers of both types and thus have a double nerve supply. The parasympathetic postganglionic neurones have their cells of origin in ganglia situated either in or close to the organ which they supply. These postganglionic fibers are therefore, as a rule, much shorter than the postganglionic fibers of the sympathetic division whose cells of origin are located in the vertebral or prevertebral ganglia. In many of the peripheral plexuses, therefore, preganglionic parasympathetic fibers are accompanied by postganglionic sympathetic fibers.

The cells of origin of the visceral efferent fibers differ from ordinary motor cells, like those in the hypoglossal nucleus, in their smaller size, less abundant cytoplasm, and smaller Nissl bodies. Cells of this type are found in the Edinger-Westphal nucleus, which gives rise to the fibers of

the third nerve that innervate through the ciliary ganglion the intrinsic musculature of the eye. Such cells are also found in the salivator nuclei which give rise to the fibers of the seventh and ninth nerves that control the flow of saliva, and in the dorsal motor nucleus of the vagus which gives rise to fibers for the thoracic and abdominal viscera. Neurones of the same type are found in the intermediolateral cell column of those segments of the cord which are associated with white rami, and in the lateral part of the gray matter of the lower sacral segments. The last mentioned group of cells gives rise to efferent fibers for the pelvic viscera.

The autonomic nervous system which we have described as the sum total of all visceral efferent neurones is by definition purely an efferent system; but this does not mean that there are not also visceral sensory fibers. These are found in great numbers in the vagus, white rami, and visceral branches of the second, third, and fourth sacral nerves. These fibers have their cells of origin in the cerebrospinal ganglia and, though they usually pass through one or more sympathetic ganglia on their way to their terminations in the viscera, they make no connections in these ganglia. Visceral reflexes, therefore, travel arcs of at least three neurones. The impulses reach the central nervous system over visceral afferent fibers and leave along preganglionic visceral efferent fibers. These end in sympathetic ganglia, and the impulses which they carry are relayed to involuntary muscle and glandular tissue by postganglionic fibers.

The ganglia, with the possible exception of those in the enteric plexuses, do not serve as reflex centers, but only as relay stations in the conduction pathways from the central nervous system to the viscera.

INNERVATION OF BLOOD VESSELS

The blood vessels of the abdominal cavity are surrounded by sympathetic nerves which branch and reunite about the vessels in such a way as to form dense plexuses. The individual strands composing these plexuses are so large that they may be seen and followed in the dissecting room. These strands are composed chiefly of unmyelinated post-ganglionic fibers from the celiac ganglion, but they contain also vagal fibers and sensory fibers from the splanchnic nerves. Around the origin of the celiac artery this network is especially dense and forms along with the two celiac ganglia the celiac plexus. From this as a central point subordinate plexuses extend in all directions along the hepatic, gastric, and splenic arteries and along the mesenteric and other branches of the abdominal aorta, and follow these vessels into the organs which they supply. A plexus accompanies the abdominal aorta and divides below into the two hypogastric plexuses which join the vesical plexus in the pelvis.

The nervous investment of the thoracic aorta is much more delicate; but in close relation to the aortic arch lie the superficial and deep cardiac plexuses from which strands are given off that accompany the coronary arteries.

It should be emphasized that the vessels of the extremities are not ac-

companied by similar plexuses. Leriche, when he advocated periarterial sympathectomy, did not realize the profound difference which exists in this respect between visceral and somatic vessels. In most instances the nerve supply for a viscus accompanies the artery and is distributed to the organ along the arterioles. But in the extremities not even the branches of the arterial tree are supplied in this way. It is true that a plexus continuous with that surrounding the aorta is found on the common iliac artery and that some bundles of fibers are continued along the external iliac to the femoral artery beyond which they cannot be followed. With the exception of these few fibers the vessels of the leg receive their innervation in an entirely different manner, namely by way of branches from neighboring somatic nerves.

In a recent study of the innervation of the vessels of the hind limb of small mammals by Woollard¹ the nerve fibers were stained with methylene blue and the entire arterial tree dissected out and arranged on a slide as a whole mount. In such a preparation he was able to trace a plexus from the aorta along iliac vessels. Individual bundles of fibers could be traced to the femoral artery where they became reduced in size and finally disappeared. The fibers in these bundles were almost all unmyelinated post-ganglionic sympathetic fibers, and for this reason these bundles could readily be distinguished from those derived as branches from adjacent somatic nerves since these twigs contained large numbers of myelinated sensory fibers.

Dr. Burns² has recently been studying the distribution of sympathetic fibers to the hind limb of the cat after complete degeneration of the somatic fibers following section of the lumbar and sacral nerves distal to the spinal ganglia. In both the cutaneous and muscular nerves of the extremity he found large numbers of unmyelinated sympathetic fibers. More than 8000 such fibers were counted in the femoral nerve alone. But in the walls of the larger vessels such as the femoral, popliteal, and anterior tibial relatively few longitudinally coursing fibers were found. His preparations support the view that the sympathetic fibers enter the limb intermingled with the somatic fibers in the nerves, from which they are given off in small twigs to the blood vessels (Figure 2). After reaching the arteries they run for relatively short distances in the nerve plexus of the adventitia before joining the terminal plexus in the media. It is, therefore, evident that periarterial sympathectomy does not denervate the peripheral vessels. In order to destroy their sympathetic innervation it is necessary to remove the sympathetic ganglionated cord or section the appropriate gray rami.

The vessels and particularly the arteries are sensitive to pain. They receive their sensory fibers from the spinal nerves (Wiedhopf³).

The cerebral vessels, like those which supply the abdominal viscera, are accompanied by plexuses of nerve fibers. Most of the fibers are unmyelinated and derived from the superior cervical sympathetic ganglion by way of the carotid plexus or from the inferior cervical ganglion by

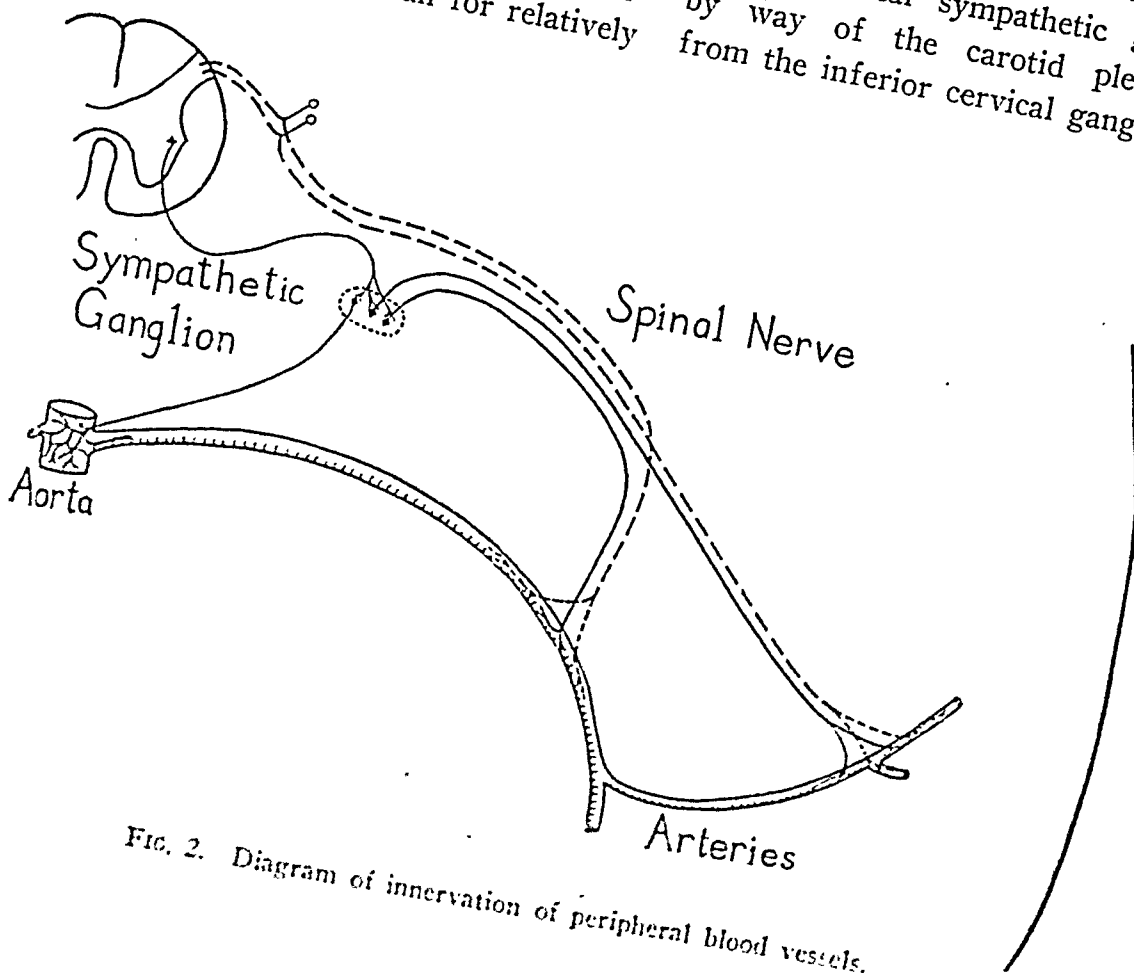


FIG. 2. Diagram of innervation of peripheral blood vessels.

way of the plexus on the vertebral artery. Some are sensory fibers derived from recurrent branches of cranial nerves and a few come in small bundles directly from the brain stem. The fibers can be followed along the small arteries and arterioles which ramify within the pia mater (Stöhr⁴). Hassin⁵ found these fibers most abundant in the pial vessels at the base of the brain, i.e., over the pons, cerebellum, medulla, and cerebral peduncles. He could not find nerve fibers following the blood vessels into the substance of the brain, and Stöhr was also of the opinion that the blood vessels within the central nervous system are not accompanied by nerve fibers. More recently Clark⁶ has been able to follow these fibers along the small arteries that penetrate into the brain substance.

Until quite recently there was no satisfactory evidence to show that intracranial blood vessels are under vasomotor control, but this now appears to have been furnished by Forbes and Wolff.⁷ They observed the pial vessels through a window set in an opening in the skull and were able to see the small arteries of the pia contract immediately after stimulation of the cervical sympathetic trunk, and dilate after stimulation of the central end of the cut vagus nerve. Many clinicians believe that cerebral vascular spasm may cause transient hemiplegia, aphasia, migraine, and convulsions. This view receives support from these recent anatomical and physiological studies of the meningeal vessels.

INNERVATION OF SKELETAL MUSCLE

I am glad to be able to tell you that the fundamental facts regarding the

innervation of skeletal muscle may be stated correctly in very simple terms, in fact in the same simple terms which were used prior to 1910. In that year Boeke⁸ described an accessory innervation of striated muscle by unmyelinated sympathetic fibers, and in a long series of subsequent papers he has attempted to support that view. Because of Boeke's recognized ability as an investigator and because his observations received more or less support from the investigations of Agduhr,⁹ Kulchitsky,¹⁰ and Kuntz,¹¹ the idea that striated muscle receives part of its innervation through sympathetic fibers came to be generally accepted. Hunter¹² and Royle¹³ by advocating sympathectomy as a measure for relief of spastic paralysis gave wide publicity to the idea that the muscles receive their tonic innervation from the sympathetic system.

But beginning with the important contribution of Hinsey¹⁴ in 1927 there have appeared during the last four years a series of papers, which have definitely shown that skeletal muscles are not innervated by sympathetic fibers, although a considerable number of such fibers is found on the intramuscular blood vessels. Hinsey, in three sets of experiments, isolated by degeneration methods the different types of fibers. First, by section of the spinal nerves distal to the spinal ganglion he caused the degeneration of all somatic fibers in the hind limb and was able to study the distribution of the sympathetic fibers. He also studied the sensory fibers after the degeneration of all motor and sympathetic elements, and the motor fibers

after degeneration of the other two types. The results of his studies are summarized graphically in figure 3. The ordinary muscle fibers receive only one type of nerve fiber, somatic motor, arising from cells in the an-

terior gray column of the spinal cord and terminating in motor end plates. The muscle spindles, which are specialized sense organs, receive both somatic motor and somatic sensory fibers. The sympathetic fibers which go to the muscles are confined to the intramuscular blood vessels. None of them end in the musculature itself.

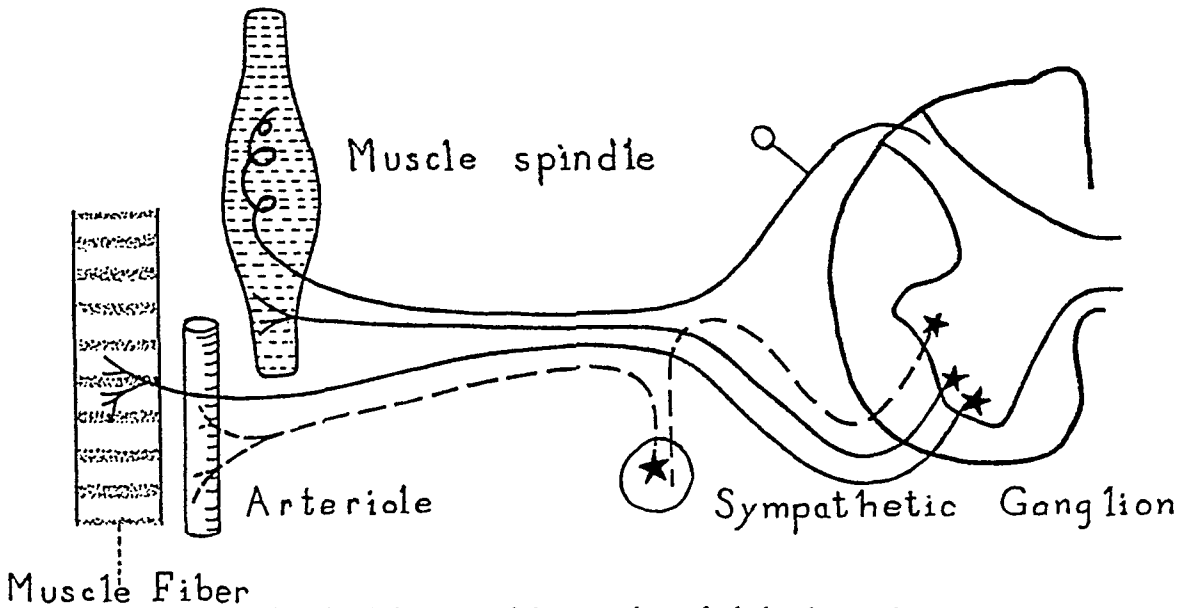


FIG. 3. Diagram of innervation of skeletal muscle.

terior gray column of the spinal cord and terminating in motor end plates. The muscle spindles, which are specialized sense organs, receive both somatic motor and somatic sensory fibers. The sympathetic fibers which go to the muscles are confined to the intramuscular blood vessels. None of them end in the musculature itself.

Wilkinson¹⁵ had the opportunity of studying Boeke's preparations and was

unable to find in them any satisfactory evidence of sympathetic accessory fibers. The most recent studies on this subject support the conclusions reached by Hinsey and Wilkinson. Tower¹⁶ found that in the mammal every end-

BIBLIOGRAPHY

- ¹WOOLLARD, H. H.: The innervation of blood vessels, *Heart*, 1926, xiii, 319-336.
- ²BURNS, B. I.: Personal communication.
- ³WIEDHOFF, O.: Der Verlauf der Gefässnerven in den Extremitäten und deren Wirkung bei der periarteriellen Sympathektomie, *Münch. med. Wchnschr.*, 1925, lxxii, 413-417.
- ⁴STÖHR, P.: Über die Innervation der Pia mater des Menschen, *Ztschr. f. d. ges. Anat.*, 1922, lxiii, 562-607.—Beobachtungen über die Innervation der Pia mater des Rückenmarkes und der Tela chorioideae beim Menschen, *Ztschr. f. d. ges. Anat.*, 1922, lxiv, 555-564.
- ⁵HASSEN, G. B.: The nerve supply of the

- cerebral blood vessels, *Proc. Assoc. Research Nerv. Ment. Dis.*, 1930, ix, 437.
- ⁶CLARK, S. L.: Innervation of the blood vessels of the medulla and spinal cord, *Jr. Comp. Neur.*, 1929, xlviii, 247-265.
- ⁷FORBES, H. S., and WOLFF, H. G.: Cerebral circulation; vasomotor control of cerebral vessels, *Arch. Neur. and Psych.*, 1928, xix, 1057-1086.
- ⁸BOEKE, J.: Die morphologische Grundlage der sympathischen Innervation der quergestreiften Muskelfasern, *Ztschr. f. Mikr.-anat. Forschung*, 1927, Bd. 8, S. 561.
- ⁹AGDUHR, E.: Sympathetic innervation of the muscles of the extremities, *Verhand. d. k. Akad. v. Wetensch. Amsterdam*, 1920, 2 sect., deel 20, p. 1.
- ¹⁰KULCHITSKY, N.: Nerve endings in the muscles of the frog, *Jr. Anat.*, 1924-1925, lix, 1-17.
- ¹¹KUNTZ, A.: On the distribution of unmyelinated fibers in muscles of the extremities following degeneration of the somatic nerves, *Anat. Rec.*, 1927, xxxv, 17.
- ¹²HUNTER, J. I.: The influence of the sympathetic nervous system in the genesis of the rigidity of striated muscle in spastic paralysis, *Surg., Gynec. and Obst.*, 1924, xxxix, 721-743.
- ¹³ROYLE, N. D.: The treatment of spastic paralysis by sympathetic ramisection, *Surg., Gynec. and Obst.*, 1924, xxxix, 701-720.
- ¹⁴HINSEY, J. C.: Some observations on the innervation of skeletal muscle of the cat, *Jr. Comp. Neur.*, 1927, xlii, 87-195.
- ¹⁵WILKINSON, H. J.: The innervation of striated muscle, *Med. Jr. Australia*, 1929, ii, 768-793.
- ¹⁶TOWER, S. S.: Further study of the sympathetic innervation to skeletal muscle; anatomical considerations, *Jr. Comp. Neur.*, 1931, liii, 177-203.
- ¹⁷WILKINSON, H. J.: Experimental studies on the innervation of striated muscle, *Jr. Comp. Neur.*, 1930, li, 129-151.
- ¹⁸HINES, M.: Studies on innervation of skeletal muscle; innervation of the extrinsic eye muscles of the rabbit, *Am. Jr. Anat.*, 1931, xlvii, 1-53.

The Functional Organization of the Involuntary Nervous System and Its Humoral Mediators*†

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WE naturally think of ourselves as air inhabiting animals, but even a slight examination would show that we are separated from the air which surrounds us by a layer of dead cells in the outer horny portion of the skin or by a layer of mucus. All that is alive within these lifeless surfaces is bathed in a salty fluid—the “*milieu interne*”, as Claude Bernard called it, or the *fluid matrix*, as we may designate it. Thus our bodies have not only the external environment which other objects have but our living parts have also an internal environment composed of the rapidly flowing blood and the more slowly flowing lymph.

In relation to the external and internal environments we may separate the nervous system into two grand divisions. The division with which we are commonly acquainted, the so-called “voluntary system”, attached to the bony skeleton, serves to change the external environment and our relations to it. This system also is supplied with surface sense organs, or exteroceptors,

serving to acquaint us with our surroundings. Since our reactions to these surroundings are directed toward objects in the outer world, we may speak of this grand division of the nervous system as the *exteroffective* system. The second grand division is the so-called “involuntary”, “vegetative”, or “autonomic” system which brings about changes in the internal environment. It may be regarded, therefore, as having *interofective* functions.

THE FUNCTIONAL CHARACTERISTICS OF THE AUTONOMIC SYSTEM

The functional characteristics of the interofective or autonomic division of the nervous system may be briefly summarized as follows.¹ Typically it innervates glands and the smooth muscles of the viscera, blood vessels, and skin. Whether it affects skeletal muscle is in question. Interposed between the smooth muscle or gland cell and the neurones reaching forth from the central nervous system there is invariably an outlying neuron, all of which is external to the central system. I have suggested¹ that this neuron may serve as an adapter or transformer of the nerve impulses so as to render them suitable for the visceral structures, which are more slowly act-

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ing than skeletal muscle. The outlying neurones, whose cell bodies are commonly gathered in ganglia, are connected with the central nervous system by three sets of outreaching neurones, making three divisions—the cranial from the brain, the sacral from the sacral cord, and the sympathetic or thoracolumbar division from the spinal cord between the brachial and lumbar enlargements. The nerve fibers of these outreaching neurones, before coming to the outlying ganglia, are called *preganglionic*. Those passing from the ganglia to the viscera are called *postganglionic*. Commonly a single viscus is doubly innervated, by neurones from the middle or thoracolumbar division and from one of the terminal divisions. Thus the heart is supplied from the cranial division by the vagus nerves and also by fibers from the ganglia of the sympathetic. As a rule in this double innervation the representatives of the two divisions are opposed in action. For example, the vagus inhibits the heart beat and the sympathetic causes acceleration.

It is typical of the cranial and sacral divisions that their preganglionic fibers, reaching from the central nervous system to the outlying neurones, end in or near the viscera which they innervate. The fibers of the vagus nerves, for instance, pass directly into the heart muscle before meeting the relay. This arrangement is such as to provide for direct and particular action of these nerves without relation to one another. Thus the contraction of the pupil by way of the third cranial nerve, the flow of saliva by way of the seventh nerve, and the slowing of the

heart by way of the tenth nerve are obviously separate and unrelated. The situation is quite different in the organization of the sympathetic or thoracolumbar division. In that division the preganglionic fibers reach out to a chain of ganglia, arranged on either side of the midline, from the superior cervical ganglion, near the corner of the jaw, through the chest and abdomen to the pelvis. These preganglionic fibers, after entering the nearest ganglion, pass through it and may reach downward or upward along the chain through two or three ganglia before coming to an end. This arrangement of the preganglionic fibers results in an overlapping of their distribution; in any ganglion there may be fibers from four or five different segments of the spinal cord. Or, to put it differently, fibers from any segment of the spinal cord may pass through four or five different ganglia of the sympathetic chain, giving off, in each one, collateral branches. This mode of organization has two effects. It greatly increases the area of distribution of the impulses coming out by any single fiber, and it also provides for diffuse distribution of impulses throughout the organism.

Confirmation of the idea that the sympathetic division is organized for diffuse distribution of effects is found in the facts that this division causes secretion of the substance adrenin into the blood, and that the circulating adrenin has practically everywhere in the body the same effects on the viscera as those produced by sympathetic impulses themselves. Obviously, even though the nerve fibers were not ar-

ranged for diffuse effects, the secreted adrenin would have such effects. The recent discovery of *sympathin*, which has, so far as we know, the same influence as adrenin, further emphasizes the view that the sympathetic division is organized for diffuse activity. In order to consider the rôle of *sympathin* it will be necessary to step back about twelve years and survey briefly the history of humoral transmission of autonomic nerve impulses.

THE HUMORAL TRANSMISSION OF VAGAL AND SYMPATHETIC IMPULSES

In 1921 Loewi² reported the observation that Ringer solution, which has been in contact with a frog heart (A), while that heart has been under the influence of the vagal nerves, acquires a new property. When applied to frog heart (B), the Ringer solution as such has the same effect as the nerve impulses, i.e., it causes inhibition of (B). Loewi also found that when the frog heart (A) is subjected to sympathetic influence, the Ringer solution in contact with it when applied to heart (B) causes acceleration. Loewi's observations have been confirmed by others and have been reported as characteristic of other hearts than that of the frog. In 1930 Finkleman³ published the interesting observation that when an excised piece of rabbit intestine (A), still supplied with its nerves, is placed so that Ringer solution which drops upon it will drip on another piece of excised rabbit intestine (B), the stimulation of the nerves of (A) causes inhibition of its spontaneous contractions and thereupon the spon-

taneous contractions of (B) are likewise inhibited. It appears that there is a substance given off from the intestine (A), when subjected to sympathetic impulses, that transfers to intestine (B) the effect of these impulses.

Further analysis of the substance produced when the vagus is stimulated has proved that it is dialyzable, that it is insensitive to acid but remarkably sensitive to alkali, and that, although quite stable while existing normally in undisturbed tissue, it becomes highly unstable when freed from such tissue by stimulation or when the tissue containing it is minced. These characteristics and also the mode of action of this "vagus substance" indicate that it is an ester of choline, and the conclusion has been drawn that it is probably acetyl choline.

The substance given off when the sympathetic supply to the heart is stimulated has many of the features of adrenin. Like adrenin it is destroyed when, after the addition of eosin, it is exposed to ultraviolet light; it is destroyed likewise by standing in air, and by being heated to boiling. It not only causes acceleration of the heart as adrenin does but also constriction of the arterioles.

The Belgian physiologist, Demoor,⁴ has criticized the inference that these substances have any physiological significance, at least as circulating substances. He pointed out that the irrigation of isolated tissues with salt solution subjects these tissues to quite unnatural conditions and that under the circumstances cell permeability may be altered in such a way that ma-

terial may escape from the cells in a manner not at all physiological. So far as the "sympathetic substance" is concerned, that criticism can now be set aside, for it has been demonstrated that a material given off from smooth muscle when subjected to sympathetic influences may be carried in the blood stream to remote structures and there have typical effects.¹² In order to bring out this evidence we must consider the use of the denervated heart as an indicator.

THE DENERVATED HEART AS AN INDICATOR OF INCREASED ADRENIN IN THE BLOOD

The heart may be wholly disconnected from the central nervous system by removing the upper thoracic sympathetic chains, by severing the right vagus nerve below the recurrent laryngeal branch (which is left to innervate the larynx), and by severing all of the cardiac branches of the left vagus trunk (which is left to control the gastrointestinal tract). Animals on which this operation is performed with careful surgical precautions live quite normally, and for many weeks there is no regrowth of nerve fibers to the heart.⁵ The heart thus denervated is highly sensitive to circulating adrenin. It responds by a faster beat when adrenin is present in the almost incredible dilution of one part in 1,400,000,000 parts of blood.⁶ By means of this sensitive signal of an increase in the concentration of adrenin in the blood stream it has been possible to show that adrenin is especially secreted when an animal is exposed to cold,⁷ when it exhibits emo-

tional excitement or exercises or moves about even slightly,⁸ when it is subjected to asphyxia,⁹ or is disturbed by hypoglycemia.¹⁰ After momentary emotional excitement, for example, the heart rate may increase immediately 70 or even 100 beats a minute.

Now, if the adrenal influence is removed by extirpation of one adrenal gland and denervation of the other, the immediate increase of heart rate after excitement disappears. But after an emotional disturbance there is still seen a delayed cardiac acceleration which reaches a maximum in about three minutes. The explanation of this phenomenon was for a long time a mysterious and tantalizing problem. This delayed increase in the rate of the denervated heart continued after extirpation of the medulla from the remaining adrenal gland, after removal of accessory adrenal tissue in front of the aorta, after the destruction of the pituitary body, and after exclusion of thyroid, parathyroid, and gonadal influences. It seemed obvious that the effect must be due to some action of the sympathetic system because that was the system most prominently concerned with emotional expression. The phenomenon still continued, however, after both abdominal chains and all of the thoracic chains except a few ganglia in the lower thorax had been removed. The natural next step, therefore, was the removal of these remnants from the thorax. When that operation was performed the phenomenon disappeared. It seemed probable, therefore, that a substance was given off into the blood stream when the sympathetic was stimulated and this

substance was the cause of the delayed increase of the heart rate.¹¹

THE PRESENCE OF SYMPATHIN AND THE ABSENCE OF "VAGUS SUB- STANCE" IN THE CIRCULATING BLOOD

Experimental proof of the surmise which has just been expressed was obtained in an animal with the heart denervated, the adrenals excluded from participation, and the spinal cord transected in the midthoracic region. The hind part of the animal was thus isolated from the fore part (i.e., the brain), and could be experimented upon, therefore, without anesthesia. By this procedure it was found that stimulation of the sympathetic fibers governing the smooth muscles of the tail hairs would cause the typical belated acceleration of the heart and, associated therewith, an increase of blood pressure.¹² The same phenomenon occurred when the smooth muscles of the hairs of a patch of skin on the flank were stimulated. A check of the blood flow into and from the tail region, and also the removal of the patch of skin on the flank, caused the stimulation to become ineffective. Furthermore, it was found that the denervated salivary glands and denervated nictitating membrane could likewise be made to exhibit characteristic activities on exciting the smooth muscles of hairs in the hind part of the body.¹³

The substance that is thus discharged from stimulated smooth muscle resembles adrenin in acting on denervated structures just as the nerve impulses themselves act and, as has been re-

cently learned, in being more effective after the injection of cocaine.¹⁴ Since the substance does not come from the adrenal glands, however, but comes from other organs when subjected to sympathetic stimulation, it has been named "sympathin". Obviously, since sympathin is given off into the blood stream and since it acts like adrenin and coöperates with adrenin in mimicking sympathetic nerve impulses, its general distribution by the blood stream supports the view that the sympathetic division of the autonomic system is normally arranged for diffuse action over the widely spread sympathetic endings.

Success in demonstrating in the blood stream the presence of a sympathetic substance naturally raised the question whether it would not be possible to demonstrate by a similar method the presence of the vagus substance. In order to test this possibility we¹⁵ used the denervated iris, submaxillary gland, and heart, as well as the denervated tongue and the normal blood pressure. We stimulated the entire distribution of the vagus nerve below the level of the heart. Furthermore, we arranged a by-pass for the portal blood so that it flowed into the inferior vena cava and thereby avoided the liver, which is destructive to acetyl choline.¹⁶ Moreover, we used a variety of anesthetics and in some experiments excluded (by operations which rendered the animal incapable of experiencing pain) the necessity of using anesthesia. In spite of these very careful and thoroughgoing efforts, all our results were negative. We obtained no

general or remote effects as a consequence of vagus stimulation. It would appear, therefore, that the parasympathetic or vagal substance has a quite local influence. This conclusion, as will be noted, is in harmony with the view that the parasympathetic innervation serves for specific and narrowly localized action and not for diffuse effects.

It is of interest to observe that the organization of the autonomic system outlined above permits all sorts of variations, both general and individual. Thus, the heart, for example, may be made to beat less rapidly or more rapidly by varying the "tone" of the vagal influence up or down, without influencing other organs having a parasympathetic supply. Or, it may be made to beat less rapidly or more rapidly by varying the "tone" of the sympathetic supply; but in this case, because of the diffuse distribution of sympathetic influences, many other organs are involved in the reaction. I have elsewhere likened the condition to that of a piano. A note may be made louder by the vigor of the blow on a single key, or many keys may be influenced by pressing on the loud or soft pedal.

THE GENERAL SERVICES OF THE AUTONOMIC SYSTEM

At the outset the statement was made that the autonomic nervous system is interofective because it regulates conditions of the internal environment. Each of its three divisions has distinctive general functions. We obtain insight into those functions by considering the circumstances under which the

several divisions are brought into action and also the effect which each produces. The sympathetic division is so specially concerned with preservation of constancy in the fluid matrix that we shall deal with it in detail. The other two divisions play an adjuvant rôle.

The functions of the *sacral division* may be summarized by the statement that they consist of a group of reflexes for emptying hollow organs which are periodically filled. Thus, sacral autonomic impulses cause contraction of the rectum and distal colon and also contraction of the urinary bladder. In both instances the effects are induced reflexly by a stretching of the tonically contracted viscera by their accumulating contents. Waste from organic activities is thereby eliminated. Distension of the seminal vesicles, though associated with more elaborate reactions, stimulates the *nervi erigentes* of the sacral division, and may thereby result in behavior which reflexly leads to a discharge of the accumulated fluid. To what degree the contractions of the distended uterus can be brought into this scheme is not quite clear. The fact that parturition can occur normally in the absence of the sympathetic division¹⁷ indicates either that there is an intrinsic government of uterine contractions which is quite adequate, or that there are influences working by way of sacral fibers which have not yet been traced.

The functions of the *cranial division*, like those of the sacral, can be summarized as mainly a group of reflexes—reflexes protective, conserva-

tive, and up-building in their service. By narrowing the pupil of the eye the cranial division protects the retina from excessive light. By providing for the flow of saliva and gastric juice and by supplying the muscular tone necessary for the periodic contractions of the alimentary canal, it assures the essential basis for proper digestion and absorption of the energy-yielding material required for all bodily activity. By vagus control of insulin secretion it may play a rôle in the storage of glycogen in the liver. Further evidence of its conservative value is seen in the assurance of time for rest and recuperation of cardiac muscle by the tonic vagal slowing of the heart rate. The cranial division, like the sacral, has uncomplicated reflexes, such as the narrowing of the pupil, and likewise activities associated with affective states. The pleasurable taste and smell of food are accompanied by the so-called "psychic" secretion of the digestive juices, and by a tonic contraction of the stomach and intestines.

The two divisions—sacral and cranial—are similar in being largely subject to interference by striated muscle. Contraction of the bladder and rectum can be aided or frustrated by impulses from the cerebral cortex, much as the reactions of the pupil can be induced or modified by voluntary acts. Indeed, as a rule, the workings of the sacral and cranial divisions involve the coöperation of the cerebrospinal nervous system to a much greater degree than do the workings of the sympathetic division, because they are much concerned with external orifices surrounded by striated muscles.

THE RÔLE OF THE SYMPATHETIC DIVISION IN STABILIZING THE INTERNAL ENVIRONMENT

In considering the services of the sympathetic division it is important to recognize the truth of the dictum laid down by Claude Bernard that just insofar as there is assurance of uniformity and stability of the internal environment, the organism is freed from the influence of changes in the external environment. The rôle of the sympathetic division of the autonomic system in governing the conditions of the internal environment can be clearly demonstrated in animals (cats, dogs, monkeys) which have had the sympathetic system entirely removed.¹⁷ Let us consider some of the phenomena exhibited by such animals as compared with normal animals.

When a normal warm-blooded animal is exposed to cold surroundings there is an erection of hairs (if the animal is provided with that covering), a contraction of surface vessels which protects from heat loss, and a discharge of extra adrenin which accelerates metabolism and thus by production of extra heat serves to keep the temperature even.⁷ Because of this arrangement for stable bodily temperature, warm-blooded animals are liberated from the limitations of inactivity that are imposed on cold-blooded animals during the winter season. Sympathectomized animals are clearly defective when exposed to cold. Pilo-motor muscles are of course not under control and therefore the hairs are not erected. The smooth muscles of the blood vessels likewise are no longer

under nervous government. Cold has no local contractile effect on either of these structures. For these reasons there is no check on the heat loss from the body. Furthermore, the organism is unable to increase the secretion of adrenin and thereby to accelerate heat production when the body temperature tends to fall. The behavior of a sympathectomized animal in cold weather is in accord with this lack of physiological efficiency. During the winter it lives almost continuously in the neighborhood of sources of heat. If placed in a cold room having a temperature near freezing, the animal undergoes a rapid drop of the body temperature which brings about vigorous shivering. Shivering is the only resource, except exercise, that is left to protect sympathectomized animals from a seriously low temperature. It is noteworthy that what is lacking in such animals is the function of the sympathico-adrenal apparatus.

Not only does the sympathico-adrenal system protect against dangers from disturbing external conditions, it also protects against possible dangers from internal changes. Thus, as can be readily shown by giving insulin, the blood sugar may be reduced to a perilous degree. If it drops from approximately 100 mgms. per cent to 45 mgms. per cent, convulsions are likely to occur, and if the condition continues coma and death result. Ordinarily no such drop in blood sugar is permitted to occur. As soon as the concentration is reduced to a degree which approximates danger the sympathico-adrenal system is brought into action and sugar is liberated from the store in the

liver.¹⁰ The value of this arrangement can be easily demonstrated in animals from which the sympathetic has been removed or in which the adrenal glands have been rendered ineffective. Such animals have no means of increasing the blood sugar when it is reduced by insulin, and in consequence are extremely sensitive to action of that agent.¹⁷

Another internal situation from which dangers may arise is that of prolonged and vigorous physical struggle. Such struggle is accompanied by a great production of heat. The extra heat, which, if allowed to accumulate, would be disastrous, is eliminated by the pouring out of sweat on the body surface and the flow of blood through the surface vessels which have been cooled by evaporation of the sweat. Sympathetic activities are here always involved. Again, prolonged vigorous effort requires sugar as a source of energy. This is set free from the liver, —again by sympathico-adrenal influences. Furthermore, there is danger from the development of acid metabolites, especially lactic acid, arising from prolonged and vigorous muscular activity. This may result in markedly defective functioning of the neuromuscular system. It can be largely avoided by an abundant supply of oxygen which is used to burn the non-volatile lactic acid into volatile carbonic acid. The volatile acid, unlike the non-volatile, is easily discharged from the body. The extra oxygen is supplied to the tissues by a faster beating of the heart, by a faster blood flow owing to an increased blood pressure from splanchnic stimulation, and by the

availability of an additional number of circulating red blood corpuscles which has been set free from storage in the spleen. In all these adjustments the sympathetic or the sympathico-adrenal system plays an essential rôle. When animals are deprived of the service of this system, the adjustments are impossible. In consequence the ability of these animals to work is greatly reduced.¹

Other illustrations might be given to show the ways in which the sympathetic division serves to keep uniform and stable the internal environment despite the potency of both external and internal disturbing conditions. Whenever the exteroceptive system goes into action and upsets the steady state which prevails in the fluid matrix while the organism is at rest, the interoceptive sympathetic system at once becomes an agent for restoration of the normal state. Unless it is overwhelmed it is quite efficient in maintaining the fitness of the internal environment for continued activity of the organism.¹⁹

THE DISTURBING EFFECTS OF EMOTIONAL EXCITEMENT

It is a matter of some moment that the bodily changes which occur in great emotional excitement are similar to those which occur in association with strenuous physical effort. The heart beats faster, the blood pressure rises, blood sugar is set free from the liver, there is a discharge of extra corpuscles from the spleen, and there may be sweating.²⁰ These striking alterations in the excited individual are best explained as preparation for action.

That is, they are an exhibition of preparedness of the sympathetic division to protect the fluid matrix in case of struggle. Probably this association of sympathetic activity with excitement has developed in the course of myriads of generations of our ancestry. In wild life, where the struggle for existence is unmitigated, the emotion of fear is associated with the instinct to flee, and the aggressive feeling of rage is associated with the instinct to attack. If there is an attack, the organism attacked must either fight back or run. If there is flight, there is likely to be pursuit. In either situation the organisms involved may be engaged in a life-or-death struggle. Obviously the preparatory alterations of the body for such struggle would be useful.

For human beings who live in civilized society, the circumstances have been largely altered. There are occasions for great excitement and for the attendant bodily changes, but relatively few occasions for the struggle which naturally follows the excitement. Actual observations on students undergoing examination have shown that they are intensely wrought up and may have an increase of blood sugar to a degree that is seen in mild diabetes. In such conditions, also, digestion may be upset, the heart may beat at an unduly fast rate, and the other changes which we have been considering may be brought about. But there is no consequent action. The body prepares for a struggle when there is no struggle to be engaged in. The whole mechanism of reinforcing the body for great effort is set at work quite uselessly. The mechanisms which would keep

the internal environment fit now act in such a way as to be really disturbing. The result is that the complex group of emotional reactions which are valuable in more primitive conditions of existence may become a real menace.

The logical treatment of such a situation as has just been described may take two different directions. The situation may be regarded reasonably and the individual may say to himself, "There is nothing that I can do; consequently I will not get excited and stirred up. Being excited is proper when there is something that requires action, but that is not now." This sug-

gestion of a rational attitude may seem an impossible counsel of perfection, but actually tests have shown that it can be made to work. If, however, it does not work and the agitation continues, the physiological mode of dealing with the situation is that of recognizing that the changes owing to excitement are directed towards efficient activity. The changes can best be met by going into action. Through sane and vigorous exercise the emotional disturbances have their natural consequences and the organism is not disturbed but is maintained in a stable state.

BIBLIOGRAPHY

- ¹CANNON, W. B.: The autonomic system; Linacre lecture, *Lancet*, 1930, i, 1109-1115.
- ²LOEWI, O.: Über humorale Übertragbarkeit der Herznervenwirkung, *Arch. f. d. ges. Physiol.*, 1921, clxxxix, 239-242.
- ³FINKLEMAN, B.: On the nature of inhibition in the intestine, *Jr. Physiol.*, 1930, lxx, 145-157.
- ⁴DEMOOR, J.: Le réglage humoral dans le coeur, *Ann. de physiol.*, 1929, v, 42-129.
- ⁵CANNON, W. B., LEWIS, J. T., and BRITTON, S. W.: Studies on conditions of activity in endocrine glands. XVII. A lasting preparation of the denervated heart for detecting internal secretion, with evidence for accessory accelerator fibers from the thoracic sympathetic chain, *Am. Jr. Physiol.*, 1926, lxxviii, 326-352.
- ⁶ANREP, G. V., and DALY, I. DE B.: The output of adrenaline in cerebral anemia as studied by means of crossed circulation, *Proc. Roy. Soc., London*, 1925, xcvi, 450-463.
- ⁷CANNON, W. B., and others: Studies on conditions of activity in endocrine glands; the rôle of adrenal secretion in chemical control of body temperature, *Am. Jr. Physiol.*, 1927, lxxix, 466-507.
- ⁸CANNON, W. B., and BRITTON, S. W.: Studies on conditions of activity in endocrine glands; the influence of motion and emotion on medullary secretion, *Am. Jr. Physiol.*, 1927, lxxix, 433-465.
- ⁹CANNON, W. B., and CARRASCO-FORMIGUERA, R.: Studies on conditions of activity in endocrine glands. XI. Further evidence for reflex and asphyxial secretion of adrenin, *Am. Jr. Physiol.*, 1922, lxi, 215-227.
- ¹⁰CANNON, W. B., McIVER, M. A., and BLISS, S. W.: Studies on conditions of activity in endocrine glands. XIII. Sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia, *Am. Jr. Physiol.*, 1924, lxxix, 46-66.
- ¹¹NEWTON, H. F., ZWEMER, R. L., and CANNON, W. B.: Studies on conditions of activity in endocrine organs; mystery of emotional acceleration of the denervated heart after exclusion of known humoral accelerators, *Am. Jr. Physiol.*, 1931, xcvi, 377-391.
- ¹²CANNON, W. B., and BACQ, Z. M.: Studies on conditions of activity in endocrine organs; hormone produced by sympathetic action on smooth muscle, *Am. Jr. Physiol.*, 1931, xcvi, 392-412.
- ¹³ROSENBLUTH, A., and CANNON, W. B.:

- Studies on conditions of activity in endocrine organs; some effects of sympathin on the nictitating membrane, *Am. Jr. Physiol.*, 1932, xcix, 398-407.
- ¹⁴ROSENBLUETH, A., and SCHLOSSBERG, T.: Sensitization of vascular response to "sympathin" by cocaine and the quantitation of "sympathin" in terms of adrenalin, *Am. Jr. Physiol.*, 1931, xcvi, 365-374.
- ¹⁵FREEMAN, N. E., PHILLIPS, R. A., and CANNON, W. B.: An unsuccessful attempt to demonstrate humoral action of "vagus substance" in the circulating blood, *Am. Jr. Physiol.*, 1931, xcvi, 435-440.
- ¹⁶HUNT, P.: Vasodilator reactions, *Am. Jr. Physiol.*, 1918, xlv, 197; 231.
- ¹⁷CANNON, W. B., and others: Some aspects of the physiology of animals surviving complete exclusion of sympathetic nerve impulses, *Am. Jr. Physiol.*, 1929, lxxxix, 84-107.
- ¹⁸DWORKIN, S.: The response of sympathectomized animals to insulin, *Am. Jr. Physiol.*, 1931, xcvi, 467-474.
- ¹⁹CANNON, W. B.: *The wisdom of the body*, 1932, W. W. Norton, New York.
- ²⁰CANNON, W. B.: *Bodily changes in pain, hunger, fear and rage*, 2 Ed., 1929, D. Appleton, New York.

The Autonomic Control of the Heart, Lungs, and Bronchi*†

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IN this presentation, the control of the heart, lungs, and bronchi by the autonomic nervous system will be considered from the clinical viewpoint. To accomplish this, it would seem permissible and, indeed, necessary to review briefly the development of the clinical conception of the subject.

HISTORICAL

Prior to 1909, although anatomical and physiological investigations on the autonomic nervous system had progressed far, there had been only occasional reference to the possible application of this knowledge to clinical medicine.^{1,2,3,4,5} Higier⁶ contends that clinicians were slow to grasp the significance of the autonomic nervous system because injury to parts of its structural mechanism usually does no great harm, whereas a similar lesion in the cerebrospinal system causes damage that attracts far more attention.

The first comprehensive attempt to apply knowledge of the autonomic nervous system to clinical medicine originated with Eppinger. He, togeth-

er with Hess,⁷ was led to believe that certain constitutional abnormalities in man were due to a heightened tone of either the parasympathetic or of the sympathetic elements of the autonomic nervous system. By the use of pharmacodynamic tests, they separated individuals giving an exaggerated response to pilocarpine, a parasympathetic stimulant, from those who appeared sensitive to adrenalin, which acts specifically on the sympathetics. To the first group, the word "vagotonia" was applied since these individuals manifested such symptoms as bradycardia, sinus arrhythmia, bronchial asthma, cardiospasm, and other disorders produced by vagus stimulation. The second group manifested symptoms of sympathetic irritability.

This attractive innovation in clinical medicine was soon followed up by other investigators^{8,9,10} and promptly found to be erroneous in that, although abnormal responses to pilocarpine and to adrenalin were noted, these usually appeared in the same subject. Consequently, the precise separation of vagotonic from sympathotonic individuals found little confirmation. Despite this refutation, the work of Eppinger and Hess proved to be of great importance in that it directed attention to

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the clinical possibilities inherent in an understanding of the autonomic nervous system. Moreover, these investigators emphasized the fact, known to physiologists for many years, that parasympathetic and sympathetic fibers innervating any given organ usually have an opposing action.

There was born, then, a rather simple and elementary clinical conception of the autonomic nervous system, based essentially on the idea that this system is made up of two elements each of which opposes the other in its action. This is still the popular clinical viewpoint, and every therapeutic measure directed at autonomic control is based on this theory.

Since Eppinger and Hess' first contribution, a voluminous bibliography dealing with the study of the autonomic nervous system in man has been built up. Obviously, methods are limited. At first, observations of the effects of various specific drugs were continued. Eventually, however, largely through physiological research, it became recognized that the results obtained were unreliable because many drugs do not have the same degree of action on all the fibers of the system tested, and some drugs are reversible in their action.¹¹ Many other findings that were determined by physiologists were applied to man. Cognizance was taken, particularly by Dr. Cannon, of the part played by the autonomic nervous system in maintaining the body economy under conditions of stress. Important information came from observations made during operative procedures on patients.

In 1926, a symposium on the auto-

nomous nervous system in man was held before the Seventh International Neurological Congress in Paris, wherein a review of the subject was presented.^{12,13} By that time it had become evident that the clinical viewpoint required revision, for it was appreciated that in many respects autonomic control in man appears to be different from that in lower animals. In man there is more variability in response to specific drugs that are used to test sympathetic and parasympathetic irritability, and controls are difficult to establish. Also, surgical procedures on the autonomic nervous system at times produce effects quite contrary to the expected. Furthermore, many pathological conditions in patients introduce new problems of autonomic nervous system behavior unmatched by experience with lower animals. Recently, attention has been paid to these facts and a more guarded attitude concerning autonomic control has developed. The discrepancies which have arisen between clinical observations and physiological understanding of the subject as yet seem to justify nothing but an open mind.

CONTROL OF THE HEART

In considering control of thoracic organs by the autonomic nervous system, emphasis is placed on the fact that this system is essentially efferent in its direction and regulatory in its action. It regulates contractions of the muscles and secretions of the glands that it innervates. It does this largely in response to afferent and central stimulation. Although afferent fibers travel within autonomic nerve trunks,

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they probably are not an integral part of the autonomic system. Consequently, this presentation is limited to the effects of efferent impulses, however they may be initiated.

The efferent nerves to the heart come from the sympathetics and from the vagus trunks. Sympathetic innervation is derived from the superior, middle and inferior cervical ganglia and the first to the fifth or sixth thoracic ganglia, from which fibers reach the two cardiac plexuses in the aortic wall. Fibers running to the heart from dorsal ganglia as low as the fifth have been discovered only recently

both in lower animals and in man.^{14,17,18} Cardiac branches from the vagi intermingle with those of the sympathetics in the cardiac plexuses and both then travel down the aorta to the heart. Although they may be traced along the coronary arteries, there is uncertainty concerning their identification in the heart wall. This is due to the presence there of intrinsic nervous tissue made up of ganglia and fibers which are difficult to differentiate from filaments of the extrinsic nerves.

Anatomical and physiological research suggests that the auricles and the auriculo-ventricular bundle are

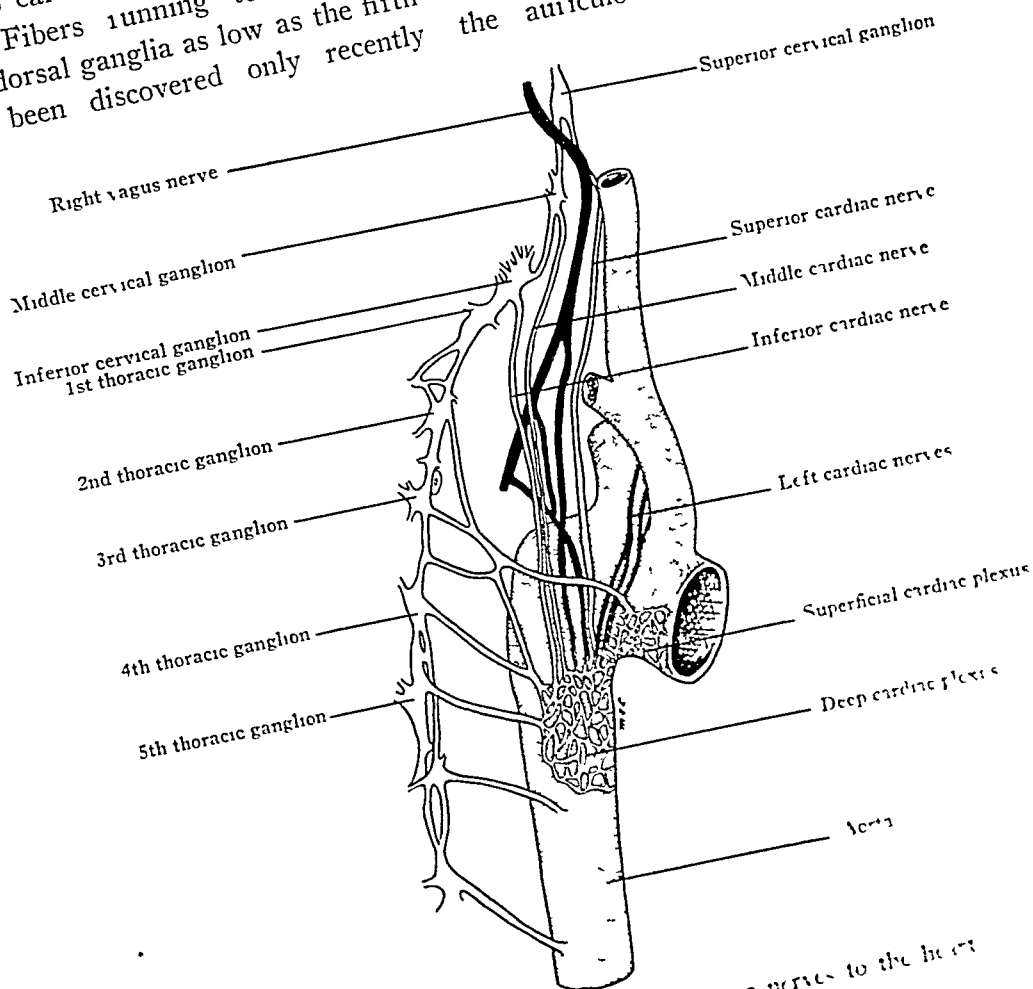


FIG 1. Schematic drawing of the extrinsic nerves to the heart

supplied both by sympathetic and parasympathetic fibers, whereas the ventricles receive largely sympathetic and little, if any, parasympathetic innervation.¹⁷ In mammals, it appears that the right vagus manifests its action mainly on the sino-auricular node (the "pacemaker"), and the left vagus particularly on the bundle of His.

The autonomic nervous system mediates impulses which modify the rate and force of the heart beats and the conductivity of cardiac muscle. In general, parasympathetic or vagus impulses slow the heart, and sympathetic impulses accelerate it. These actions are influenced by drugs and physical agents, a fact made much use of in therapeutic considerations of various abnormalities of cardiac action. Lewis¹⁸ states that in man far more is known concerning the vagus participation in these processes than is known of the rôle of the sympathetics.

INFLUENCE ON HEART RATE

In particular, various abnormalities in rate and rhythm are influenced by the autonomic nerve impulses to the heart. Several examples may be stated. In congestive heart failure, digitalis slows the rate not only by increasing the tone and contractility of cardiac muscle, but also by stimulating the vagus both centrally and peripherally. As a result, the sino-auricular node reduces its tempo and the vagus fibers in the bundle of His serve as a brake to auricular impulses on their way to the ventricles. Relief of paroxysmal tachycardia by pressure over the vagus nerve in the neck is due presumably to a flooding of the auricle with inhibi-

tory impulses. The ectopic focus temporarily loses its irritability, which permits the pacemaker again to resume control and normal rhythm to become reëstablished. Although vagus pressure in the neck may be, in reality, a carotid sinus effect,¹⁹ pressure over the eyeball, which often achieves the same result, doubtless acts reflexly through vagus stimulation. Of interest is a recent observation that pressure over the right vagus slows the heart more effectively than pressure over the left. The explanation offered is that the right vagus, particularly, influences the pacemaker.

The tachycardia of organically normal hearts, that occurs during fright and other emotional disturbances, is known to be due largely to sympathetic stimulation from adrenal secretion.²⁰ Of interest, in this connection, is the type of heart action that is seen in patients with so-called "effort syndrome". Many of these individuals have a tachycardia; others have an abnormally slow heart. Fraser and Wilson²¹ tested a group of such patients with small doses of pilocarpine and adrenalin and obtained an exaggerated response to each. Such a reaction has been considered by many to represent an autonomic imbalance which clinically presents symptoms and signs that are usually interpreted as a neurosis.

In cases of tachycardia not associated with congestive heart failure, there is no drug which will adequately slow the rate through vagus stimulation. No parasympathetic hormone analogous to adrenalin has as yet been definitely demonstrated, although

Loewi²² has shown that a parasympathetic stimulant may exist. Such drugs as pilocarpine, physostigmine, and apomorphine either exert their influence more on parasympathetic fibers elsewhere than on those of the heart, or side effects prevent their routine use. Acetyl choline is a powerful parasympathetic stimulant; and a choline derivative has been used by Stepp²³ with effect in cases of paroxysmal tachycardia. As yet, however, choline derivatives have not found therapeutic favor.

When bradycardia occurs in the presence of organic heart disease, it is almost always due to heart block. Under these circumstances, especially in complete block, advantage has been taken of the fact that the ventricles have sympathetic innervation, and temporary benefit from the use of adrenalin has been reported.^{24,25} In organic heart disease, digitalis may bring on heart block through its action on the vagus. In these cases, release may be secured with atropin. Although experimentally heart block may result from vagus stimulation alone, this is a questionable clinical manifestation.²⁶

Bradycardia in the absence of heart disease is essentially parasympathetic in origin. This is exemplified by its appearance in convalescence, in youth, and in intracranial pressure wherein the vagus presumably is stimulated centrally. Cardiac arrhythmias of vagus origin are well known. Lewis²⁷ recognizes a vagus effect wherein there is an abrupt and profound slowing of the heart, associated with an independent lowering of blood pressure. This

combined disturbance is often responsible for attacks of faintness and actual loss of consciousness. According to Lewis, it is, by far, the commonest cause of fainting attacks in both men and women, and occurs both in individuals otherwise healthy and in those who suffer from heart disease in its several forms.

ANGINA PECTORIS

The autonomic nervous system is involved either directly or reflexly in cardiac abnormalities other than disturbances in rate and rhythm. Of particular clinical interest in recent years, has been the rôle of the autonomic nerves in angina pectoris. Various procedures designed to block both efferent and afferent pathways in this condition have produced a wealth of data, much of which is difficult to interpret. A particular handicap is our lack of accurate knowledge concerning the source of pain. The successful results obtained by removing the lower two left cervical sympathetic ganglia, and by injecting alcohol and procaine about the thoracic ganglia, may be attributed merely to an interruption of pain impulses traveling from the heart through or near to these structures. This implies no participation of autonomic fibers.

There are instances, however, where it appears that sympathetic stimulation influences the pain of angina pectoris. Leriche²⁸ isolated the lower portion of the left cervical sympathetic chain in a patient who had never had angina. Electrical stimulation and pinching of the left inferior cervical sympathetic ganglion caused an intense pain over the precordium in the second and third

intercostal spaces. Novocainization of the ganglion prevented this effect. It is interesting that in two similar patients, stimulation of the superior pole of the ganglion provoked a very intense radiation of the pain into the arm of the corresponding side; whereas when the lower half was stimulated, the precordial region was most affected. In still another patient subject to angina pectoris, an attack occurred before the stellate ganglion had been completely exposed. Infiltration with novocaine about the ganglion produced immediate cessation of pain. Although it is quite possible in this instance that novocaine blocked pain impulses traveling to the cord, it is difficult to interpret the results in the other cases. Possibly electrical stimulation of the lower cervical sympathetic ganglion overflowed into contiguous afferent

nerves, but one would hardly expect to excite afferent impulses from the arm in this location.

Another clinical indication of the possible participation of efferent fibers in angina pectoris is the relief of pain that has resulted after removal of the superior cervical sympathetic ganglion alone.²⁹ Although sensory fibers are found high in the sympathetic chain,³⁰ fibers in the superior cardiac nerve from this ganglion are largely efferent. There has been a sufficient number of successful results in angina pectoris from superior cervical ganglionectomies to warrant attention.^{31,32} The implication has been that in patients so relieved, efferent impulses from the superior cervical ganglion produced a peripheral effect that caused precordial pain. As an explanation, it has been suggested repeatedly³³ that the superior

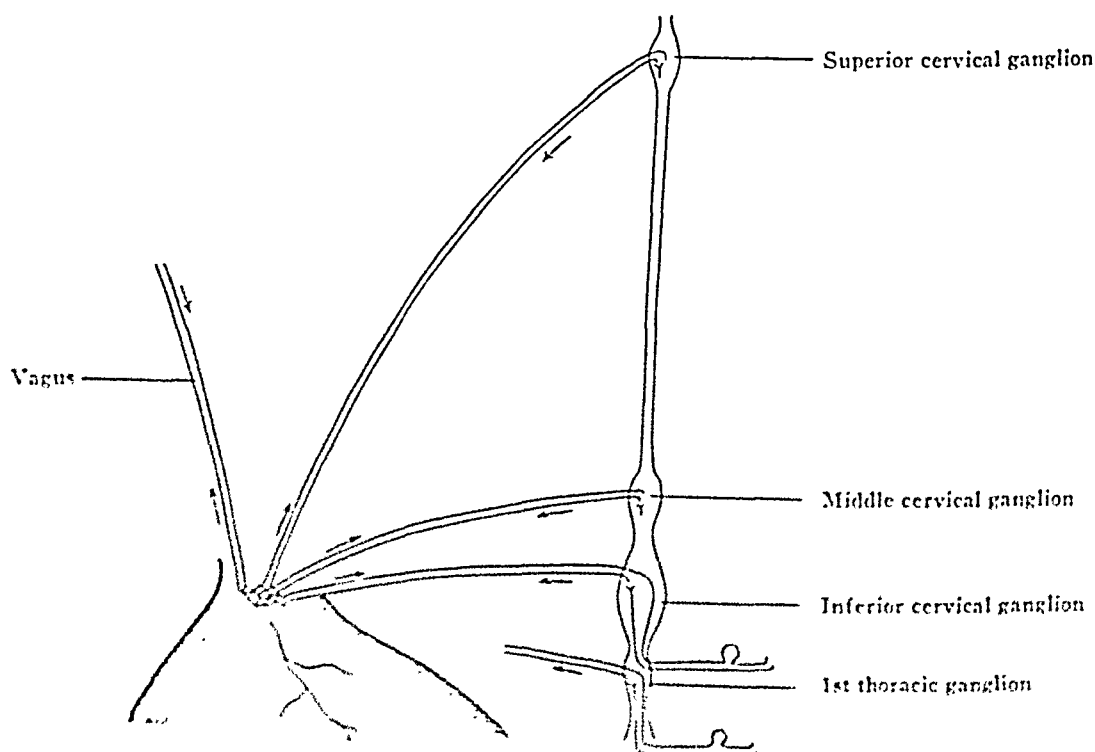


FIG. 2. Schematic representation of nerve pathways from the cervical ganglion to the heart.

cardiac nerve carries vasomotor fibers to the coronary arteries, and that sympathetic stimulation causes coronary spasm. A disturbing element of this theory, however, lies in the fact that numerous investigators^{34,35,36,37} agree that in mammals, at least, sympathetic stimulation does not cause constriction of the coronary arteries, but dilatation, whereas it is vagus stimulation that induces contraction.

If angina pectoris be due to coronary spasm, then cervical sympathectomy for its relief, although successful clinically in many cases, is a highly illogical procedure according to physiological experimentation. The answer to this riddle must await further knowledge of the autonomic nervous system in man and, especially, of how it functions in disease.

CONTROL OF THE LUNGS

The autonomic nervous system controls the lungs largely through its action on the bronchi. Parasympathetic

monary plexuses which communicate. From these plexuses, fibers follow the bronchi and bronchial vessels in their ramifications far down into the lungs in an elaborate intrinsic system of networks in which many small ganglia appear.

There is general uniformity of opinion that peripheral vagus stimulation causes bronchoconstriction, and recently it has been shown that mucous secretion from the bronchial glands occurs also.³⁸ Vagus stimulation likewise inhibits constriction of the bronchial vasculature. Sympathetic stimulation, on the other hand, brings on bronchial dilatation, diminished mucous secretion, and constriction of the bronchial vessels. There is little evidence that the autonomic nervous system exerts important vasomotor control over the pulmonary vessels. This does not hold true for the bronchial artery which is derived from the aorta. Schematically, autonomic control of the lungs is represented as follows:

TABLE I

Bronchial	Vagus Stimulation	Sympathetic Stimulation
Muscles	Contraction	Relaxation
Glands	Secretion	Inhibition
Vessels	Dilatation	Constriction

innervation is derived from the pulmonary branches of the vagus nerves, and sympathetic impulses arise in the second, third, and fourth thoracic ganglia. Both vagus and sympathetic fibers intermingle at the roots of the lungs to form the anterior and posterior pul-

Although normal respiration is essentially a voluntary process involving cerebrospinal nerve impulses, yet respiratory movements are subject to voluntary control only within limits. It has long been known that the vagus has an influence over the process of

breathing.³⁹ Section of both vagi in the neck immediately increases the amplitude of inspiration and retards the rate. There is little doubt that vagus section interrupts afferent impulses which influence respiratory movements through central action. Whether any important efferent fibers necessary to normal respiration are affected, is a moot question. Recently, much evidence has been presented to indicate that the bronchial muscles contract during expiration and thus assist in expelling air from the lungs. Miller,⁴⁰ from his reconstruction models of the bronchi, thought this to be so. Hudson,⁴¹ by serial X-ray studies, believes that a peristaltic motion of the bronchi during breathing can be visualized. Luisada,⁴² by placing an electrode far down the bronchial tree, has secured electrical tracings which, he presumes, record action currents in the bronchial muscles during respiration. He terms these tracings "Electrobronchograms". They show a definite vagus effect during expiration which has been found in man as well as in lower animals. Heinbecker⁴³ and Mac-lin⁴⁴ also believe that during inspiration the bronchi lengthen and, at the same time, widen. Although it would appear that these actions involve efferent nerve impulses, it has been suggested that the numerous ganglia within the bronchial walls may, in part, initiate muscular movement. Until further information on this interesting process becomes available, one must consider the question of control of respiration through efferent nerve fibers as yet unanswered.

PULMONARY DISORDERS

The autonomic nervous system participates reflexly in many diseases of the lungs and bronchi. This is exemplified by such reflex manifestations as digestive disturbances and bradycardia,⁴⁵ that occur in pulmonary disorders. Likewise, in asphyxia, the autonomic nervous system is called into play to widen the bronchi through sympathetic stimulation, and thereby facilitate breathing.⁴⁶ An outstanding example of autonomic disturbance is bronchial asthma.

For years, there had been controversy as to whether an asthmatic paroxysm was due to spasm of the bronchial muscles, to edema of the bronchial mucosa, or to hypersecretion of the bronchial glands. With a better understanding of the control of bronchial structures through the autonomic nervous system, it became apparent that all three factors play a part, for each results from vagus stimulation. (Table I) In allergic asthma, it appears that an attack is initiated by direct stimulation of the nerve endings in the bronchi, whereas in so-called emotional asthma, nasal asthma, and other reflex asthmas, impulses travel through the vagus nucleus to the bronchial muscles, blood vessels, and glands. Of interest is the fact that patients with bronchial asthma have been shown to give exaggerated responses both to pilocarpine and to adrenalin.⁴⁷ This indication of autonomic imbalance is probably responsible for the theory that asthma is essentially a neurosis. Since an asthmatic attack appears to be entirely a vagus

or parasympathetic effect, one would predict that adrenalin, through its powerful stimulating action on the sympathetics, should be a useful therapeutic drug. That this is so, is well known. Atropin, by paralyzing vagus nerve endings, is likewise effective, but it must be given in doses far larger than those ordinarily employed.

As surgery of the autonomic system developed, it came to be applied to cases of bronchial asthma, and considerable data on this type of treatment has accumulated.⁴⁸ The results of vagus nerve section have been indifferent. This, perhaps, is the expected result. Cases of reflex asthma should be helped by this procedure, for efferent impulses descending from the vagus nuclei are interrupted. In allergic asthma in which vagus nerve endings are stimulated directly, section of the nerve trunk would not be expected to cause immediate cessation of attacks, at least, not until the distal end of the nerve had degenerated. Cervical sympathectomies for the relief of bronchial asthma have been performed in many cases. Inasmuch as asthma is evidently a vagus effect which is controlled by sympathetic stimulation, destruction of sympathetic pathways appears to be a very unreasonable pro-

cedure. Moreover, since sympathetic control of the bronchi is derived from the second, third, and fourth thoracic ganglia, one is at a loss to explain the possible effect of cervical ganglionectomy. The surprising fact is that this operation, beyond question, has been proven to be of benefit in many cases.

From this, one may infer that our understanding of the mechanism of an asthmatic attack is incomplete. It is more probable that our ideas concerning the behavior of the autonomic nervous system in man, and especially in disease, are elementary. To make them more complete, it becomes necessary to study human response in each instance where data derived from animal experimentation is applied directly to man. Consequently, the clinical approach to the subject is developing more and more into an effort to explain phenomena actually observed by operation and at the bedside. These methods of study have already revealed facts which may prove to be of much significance. They offer promise of increasing contributions to the wealth of knowledge of the autonomic nervous system already assembled through anatomical and physiological research.

REFERENCES

- ¹NOTHNAGEL, H.: Angina Pectoris vasomotoria, *Deutsch. Arch. f. klin. Med.*, 1867, iii, 309.
- ²CURSCHMANN, H.: Über vasomotorische Krampfzustände bei echter Angina Pectoris, *Deutsch. med. Wchnschr.*, 1906, xxxii, 1527-1531.
- ³E.: Die Funktionsprüfung der
beim Menschen, Münch.
- ⁴BEER, T.: Über den Einfluss der peripheren Vagusreizung auf die Lunge, *Arch. f. Physiol.*, 1892, Suppl.-Bd., 101-216.
- ⁵DIXON, W. E., and BRODIE, T. G.: Contributions to the physiology of the lungs. Part I. The bronchial muscles, their innervation, and the action of the
J. Physiol., 1911, xiv, 1-11.

- ⁶HIGIER, H.: Vegetative neurology; the anatomy, physiology, pharmaco-dynamics and pathology of the sympathetic and autonomic nervous systems, 1919, Nervous and Mental Disease Publishing Company, New York and Washington.
- ⁷EPPINGER, H., and HESS, L.: Zur Pathologie des vegetativen Nervensystems, Ztschr. f. klin. Med., 1909, lxvi, 345-351; lxxviii, 205, 230.
- ⁸PETRÉN, K., and THORLING, I.: Untersuchungen über das Vorkommen von Vagotonus und Sympathikotonus, Ztschr. f. klin. Med., 1911, lxxiii, 27-46.
- ⁹BARKER, L. F., and SLADEN, F. J.: The clinical analysis of some disturbances of the autonomic nervous system, with comments upon the so-called vago-tonic and sympathetico-tonic states, Trans. Assoc. Am. Phys., 1912, xxvii, 471-502.
- ¹⁰BAUER, J.: Zur Funktionsprüfung des vegetativen Nervensystems, Deutsch. Arch. f. klin. Med., 1912, cvii, 39-102.
- ¹¹SOLLMANN, T.: The pharmacology of the autonomic system, Physiol. Rev., 1922, ii, 479-504.
- ¹²ANDRÉ-THOMAS: Les moyens d'exploration du système sympathique et leur valeur, Rev. neurol., 1926, i, 767.
- ¹³SÖDERBERGH, G.: Sur les moyens actuels d'exploration du système sympathique en clinique et leur valeur, Rev. neurol., 1926, xxxiii, 721-766.
- ¹⁴JONESCO, D., and ENACHESCO, M.: Nerfs cardiaques naissant de la chaîne thoracique du sympathique, au-dessous du ganglion stellaire. Les nerfs cardiaques thoraciques chez quelques mammifères, Compt. rend. Soc. de biol., 1927, xcvii, 977-980.
- ¹⁵CANNON, W. B., LEWIS, J. T., and BRITTON, S. W.: Studies on the conditions of activity in endocrine glands. XVII. A lasting preparation of the denervated heart for detecting internal secretion, with evidence for accessory accelerator fibers from the thoracic sympathetic chain, Am. Jr. Physiol., 1927, lxxvii, 326-352.
- ¹⁶KUNTZ, A.: The autonomic nervous system, 1929, Lea & Febiger, Philadelphia, 135.
- ¹⁷CUNNINGHAM, W., and TETTER, E.: Distribution of nerves in the heart, Jr. Physiol., 1913, xlvii, 141-150.
- ¹⁸LEWIS, T.: Clinical disorders of the heart beat, 1925, Shaw & Sons, London, 8.
- ¹⁹HEYMANS, C., BOUCKAERT, J. J., and DAUTREBANDE, L.: Sinus carotidien et réflexes respiratoires; influences respiratoires réflexes de l'acidose, de l'alcalose, de l'anhydride carbonique, de l'ion hydrogène et de l'anoxémie. Sinus carotidiens et échanges respiratoires dans les poumons et au delà des poumons, Arch. internat. de pharmacodyn. et de thérapie, 1930, xxxix, 400-448.
- ²⁰CANNON, W. B.: Bodily changes in pain, hunger, fear, and rage, 2 ed., 1929, Appleton & Co., New York.
- ²¹FRASER, F., and WILSON, R. M.: The sympathetic nervous system and the "irritable heart of soldiers", Brit. Med. Jr., 1918, ii, 27-29.
- ²²LOEWI, O.: Über humorale Übertragbarkeit der Herznervenwirkung. II., Arch. f. d. ges. Physiol., 1921, cxiii, 201-213.
- ²³STIEFF, W., and SCHLIEPHAKE, E.: Cholin bei paroxysmaler Tachykardie, Münch. med. Wchnschr., 1925, lxxii, 1997-1999.
- ²⁴PHEAR, A. G., and PARKINSON, J.: Adrenalin in the Stokes-Adams syndrome, Lancet, 1922, i, 933-936.
- ²⁵DE GRAFF, A. C., and WEISS, S.: Observations on the extrinsic nervous control of the auricles and ventricles in complete auriculo-ventricular block in man, Jr. Clin. Invest., 1925, ii, 227-244.
- ²⁶BOURNE, G.: Notes on a case of heart-block whose grade was decreased by an inspiratory increase in sympathetic tone, St. Barth. Hosp. Rep., 1928, lxi, 146-153.
- ²⁷LEWIS, T.: Clinical disorders of the heart beat, 1925, Shaw & Sons, London, 14.
- ²⁸LERICHE, R.: Recherches expérimentales sur l'angine de poitrine, Presse méd., 1925, xxxiii, 1361.
- ²⁹CORFEE, W. B., and BROWN, P. K.: The surgical treatment of angina pectoris, Arch. Int. Med. 1923, xxxi, 200-220.
- ³⁰HEINBECKER, P.: Recent advances in our knowledge of the autonomic nervous system, Jr. Thorac. Surg., 1932, i, 233-242.
- ³¹CORFEE, W. B., BROWN, P. K., and HUM-

- BER, J. D.: Angina pectoris, 1927, Tulane University Press, New Orleans.
- ³²CUTLER, E. C.: Summary of experiences up-to-date in the surgical treatment of angina pectoris, *Am. Jr. Med. Sci.*, 1927, clxxiii, 613-624.
- ³³HOLMES, W. H., and RANSON, S. W.: Cervical sympathectomy in angina pectoris; with report of a case, *Jr. Lab. and Clin. Med.*, 1924, x, 183-189.
- ³⁴MAAS, P.: Experimentelle Untersuchungen über die Innervation der Kranzgefäße des Säugethierherzens, *Arch. f. d. ges. Physiol.*, 1899, lxxiv, 281.
- ³⁵WIGGERS, C. J.: The innervation of the coronary vessels, *Am. Jr. Physiol.*, 1909, xxiv, 391-405.
- ³⁶ANREP, G. V., and SEGALL, H. N.: The regulation of the coronary circulation, *Heart*, 1926, xiii, 239-260.
- ³⁷GREENE, C. W.: An analysis of the efferent pathways and vasomotor control of the coronary circulation in the dog, *Am. Jr. Physiol.*, 1931, xcvi, 526.
- ³⁸KOUNTZ, W. B., and KOENIG, K.: Studies of bronchial secretion, *Jr. Allergy*, 1930, i, 429-433.
- ³⁹RECHT, G.: Dyspnoë beim Vagusdruckversuch, *Klin. Wchnschr.*, 1924, iii, 916-920.
- ⁴⁰MILLER, W. S.: The musculature of the finer divisions of the bronchial tree and its relation to certain pathological conditions, *Am. Rev. Tuberc.*, 1922, v, 689-704.
- ⁴¹HUDSON, W. A., and JARRE, H. A.: Functional studies of the tracheo-bronchial tree, with the aid of the cin-ex camera, *Brit. Jr. Radiol.*, 1929, ii, 523-533.
- ⁴²LUISADA, A.: Die Lunge als contractiles Organ. Eine neue Methode zur Untersuchung der glatten Muskeln der Lunge, *Beitr. z. Klinik. d. Tuberk.*, 1930, lxxiii, 657-687; 1931, lxxvii, 460-470.
- ⁴³HEINBECKER, P.: Method for demonstration of calibre changes in bronchi in normal respiration, *Jr. Clin. Invest.*, 1927, iv, 459-469.
- ⁴⁴MACLIN, C. C.: The musculature of the bronchi and lungs, *Physiol. Rev.*, 1929, ix, 1-60.
- ⁴⁵POTTENGER, F. M.: The vegetative nervous system, 1930, Williams and Wilkins, Baltimore, 587.
- ⁴⁶BROWN, W. L.: The rôle of the sympathetic nervous system in disease, *Lancet*, 1919, i, 827; 873.
- ⁴⁷ALEXANDER, H. L., and PADDOCK, R.: Bronchial asthma: response to pilocarpine and epinephrine, *Arch. Int. Med.*, 1921, xxvii, 184-191.
- ⁴⁸PHILLIPS, E. W., and SCOTT, W. J. M.: The surgical treatment of bronchial asthma, *Arch. Surg.*, 1929, xix, 1425-1456.

The Results of Sympathectomy in the Treatment of Peripheral Vascular Diseases, Hirschsprung's Disease, and Cord Bladder*†

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SYMPATHECTOMY in its various forms is growing in its field of usefulness as our knowledge of the physiology of the autonomic nervous system is increased. The altered function of this nervous system gives rise to and determines the course of many diseases; for, in addition to carrying afferent pain fibers, the autonomic nervous system influences blood flow, smooth muscle activity and glandular function. The correlation of disease with its anatomic and physiologic aspects may give rise to various opinions; hence, one should analyze carefully all facts before advocating or condemning the newer ideas concerning the disease and the method of treatment. Progress has been made in the surgical treatment of angina pectoris, spastic lesions in striated muscles, and trophic and painful lesions of the extremities. Most satisfactory results have been accomplished by sympathetic ganglionectomy and trunk resection in the treatment of peripheral vascular diseases, such as Raynaud's

disease,^{1-5,16,20,22,26} thromboangiitis obliterans^{2,22,26} with vasomotor spasm of the collateral arteries, acral scleroderma^{7,17} developing subsequent to Raynaud's disease, and periarticular arthritis^{8,8,9,31,60,61,62} in the hands and feet, associated with vasospastic phenomena of cold, clammy, pale, and cyanotic extremities. The sectioning of sympathetic fibers to the internal sphincter muscles of the rectum and bladder,^{30,57,72,73} and of sympathetic fibers carrying inhibitory impulses to the large bowel and to the detrusor muscles of the bladder has materially aided the expulsive forces of both the rectum and bladder, thus offering assistance in the treatment of congenital megacolon and cord bladder.^{43,44} Trophic changes of both organs are likewise improved, since vasomotor fibers which are intermingled with the presacral and mesenteric nerves are also necessarily sectional.

Numerous studies are being carried on by various investigators in the hope of relieving visceral pain,^{10,25,34,63} malignant hypertension,⁵⁹ asthma,^{50,52} retinitis pigmentosa,⁶⁷ optic atrophy, nephritic conditions,^{30,62} cardiospasm, pylorospasm,⁴⁴ and of influencing endocrine secretions. Many of these

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endeavors will probably be fruitless but it is fair to assume that a central influence, acting through the autonomic nervous system, is directly or indirectly responsible for the production of these diseases.

I shall not attempt to analyze in detail my colleagues' and my own experience in the treatment of these various disorders, for this would necessitate the inclusion of a rather large series of cases, which have been previously reported by various members of the staff of The Mayo Clinic.

ANATOMY

The sympathetic nervous system is an aggregation of ganglia, nerves, and plexuses through which the viscera, glands, heart, blood vessels, and smooth muscles in other situations receive their innervation. The most conspicuous feature of the system is a pair of ganglionated nerve cords, or sympathetic trunks, which extend vertically through the neck, thorax, and abdomen. Each sympathetic trunk is composed of a series of ganglia bound together by short nerve strands. Every spinal nerve is connected with the sympathetic trunk of its own side by one or more gray rami communicantes through which it receives sympathetic fibers for the control of blood vessels, of sweat glands, and of the smooth muscle of the hair follicles situated within the territory of its distribution. The majority of the nerve fibers that take origin in the ganglia of the sympathetic chain are distributed through the gray rami and the spinal nerves.

The thoracic and upper lumbar nerves are connected with the sympathetic chain by white as well as gray rami communicantes. These white rami contain both afferent and efferent fibers. The latter take origin from cells in the gray matter of the spinal cord, travel through the ventral root and white rami, and enter the sympathetic system to terminate in synaptic relation with the nerve cells found in the sympathetic ganglia. They are often designated as preganglionic fibers, while those fibers which arise in the ganglia

and relay the impulses onward are called postganglionic. The gray rami contain postganglionic fibers and the white rami, preganglionic fibers.

The majority of the preganglionic fibers turn either upward or downward in the sympathetic chain, and run for varying distances within it before ending in its ganglia. The cervical sympathetic trunk is composed exclusively of preganglionic efferent fibers, derived through the white rami from the upper thoracic nerves and ascending to terminate in the cervical sympathetic ganglia. The lumbar and sacral portions of the trunk are composed in the major part of descending fibers derived through the white rami from the lower thoracic and upper lumbar spinal nerves.

Those fibers of the white rami which are concerned with the innervation of the abdominal viscera pass into the splanchnic nerves and end in the celiac ganglion. They reach the splanchnic nerves after passing through the lower half of the thoracic sympathetic chain, but they are not interrupted in the chain ganglia through which they pass. They eventually reach the viscera by following the arterial supply to these organs, or by direct extension as postganglionic fibers from the various plexiform arrangements or sympathetic ganglia. The thoracic viscera receive their postganglionic sympathetic rami from the upper thoracic sympathetic chain in a similar arrangement.

The autonomic nervous system, in addition to the sympathetic thoracolumbar outflow, contains two streams of preganglionic visceral efferent fibers called the parasympathetic system; the cranial stream arises from the third, seventh, ninth and tenth cranial nerves, the sacral stream from the second, third, and fourth sacral nerves.

According to Ranson, and Kuntz,⁴¹ most of the sympathetic nerves contain, in addition to the fibers already considered, sensory fibers which convey impulses from the viscera to the spinal cord. These sensory fibers have their cells of origin in the spinal ganglia and reach the sympathetic system by way of the white rami. Visceral reflexes therefore travel arcs of at least three neurons each. The impulses reach the spinal cord along visceral afferent fibers through

white rami and the dorsal roots. These afferent sympathetic fibers end in sympathetic ganglia, and the impulses which they carry are relayed to involuntary muscle and glandular tissue by postganglionic fibers. The ganglia of the sympathetic trunk do not serve as reflex centers, but only as relay stations⁵² in the conduction pathways from the spinal cord to the viscera.

The vasomotor innervation of the arteries of the extremities and of the trunk was once believed to be centrifugal⁴⁶ in its arrangement, but the work of Kramer and Todd, and Potts has proved rather conclusively that the distribution corresponds to the musculo-cutaneous somatic distribution, except for short distances where the principal arteries leave the aorta. Therefore, it is apparent that complete vasodilating effects are accomplished only when all vasomotor fibers are interrupted by section of a sympathetic trunk, by ganglionectomy, or by complete ramisection.

SURGICAL PROCEDURES

Surgical procedures affecting the sympathetic nervous system date back to 1899, when Jaboulay attempted to relieve painful conditions of the lower extremities by performing periarterial sympathectomy. This procedure was not given serious consideration until Leriche reported his experiences in 1913, when he advocated periarterial sympathectomy for numerous peripheral vascular, trophic, and painful lesions. Following his teaching many surgeons became interested in the subject of sympathectomy and employed his procedure for similar lesions in addition to attempting the treatment, by sympathectomy, of exophthalmic goiter, glaucoma, and epilepsy. Jonnesco removed the stellate ganglion for angina pectoris by the anterior-superior approach with moderate success. In 1923 Brüning employed Jonnesco's operation in the treatment of one case of Raynaud's disease and one case of scleroderma, both of the upper extremities, and reported success. Unfortunately, a similar good result has not been obtained by other surgeons, including myself. It is true that periarterial sympathectomy and removal of the stellate ganglion by the Jonnesco method did afford some relief of symptoms and

improvement of the circulation but it failed to give complete relief.⁴⁶

Royle⁶³ in 1924 advocated and performed ramisection for relief of spasticity of the muscles of the extremities, but difficulty was encountered in duplicating his results. I have obtained some reduction of the spasticity by abdominal transperitoneal lumbar sympathetic ganglionectomy and trunk resection, which I first performed May 20, 1924. I am inclined to believe, however, that the results are due to the increased blood supply following thorough interruption of vasomotor fibers, rather than to section of sympathetic nerves to striated muscle, for numerous investigators doubt the existence of sympathetic innervation of striated muscle in mammals.

Orbeli believes that the sympathetic fibers augment cerebrospinal responses. Von Gaza in 1924, Archibald in 1928, and Scrimger in 1929 performed, with some success, paravertebral ramisection of the splanchnic nerves for visceral pain. This problem is undergoing much investigation at this time.

Davis and Kanavel,²¹ and I were among those who attempted to duplicate the results Royle reported in 1924. On May 20, 1924, I employed the method mentioned above, and it was following this that I observed that the temperature of the skin of the lower extremities remained permanently increased. Royle reported that the cutaneous temperatures in the first case in which he performed ramisection were increased only temporarily, but later stated that a slight increase remained permanently. This suggested that the more extensive operation of ganglionectomy and trunk resection included all of the vasomotor fibers to the extremities. This phenomenon reopened the field of surgical treatment of peripheral vascular diseases. Davis and Kanavel, Diez, and Fulton subsequently reported experiences similar to mine following ganglionectomy and trunk resection.

In 1924 preoperative and postoperative calorimetric studies were made by Brown¹⁵ of patients on whose sympathetic apparatus I operated for spastic conditions. The report showed that following operation elimination of heat had increased on an average of 400 per cent, and that this increase had remained permanent. These data suggested

the practicability of applying surgical procedures in vasospastic diseases, and I performed such an operation with success on March 19, 1925, in a case of Raynaud's disease of the lower extremities. Subsequent study of this patient and of others has shown that vasodilatation has remained, and that the patients have been free from all symptoms. I first carried out cervicothoracic ganglionectomy and trunk resection by the posterior approach on July 31, 1928. Following success in the treatment of Raynaud's disease patients with other diseases in which vasospastic phenomena were manifested were likewise subjected to the operation. It was necessary, however, before such operations could be undertaken that some method be provided of determining preoperatively the degree of vasomotor spasm present and whether sufficient relaxation of this spasm was possible to justify the employment of surgical procedures to secure such relaxation.

Brown¹⁴ found that some aid in answering these questions could be obtained from the study of capillary behavior in the affected extremities but that a more reliable *vasomotor index* resulted from determination of the possible variations in blood flow to the extremity as indicated by variations in the skin temperature under standard conditions. Therefore, Brown¹⁵ introduced studies of cutaneous temperature as a vasomotor index, arguing that unless the peripheral cutaneous temperature could be increased 3°C. by regional or spinal anesthesia or increased two or more times the increase of the mouth temperature following intravenous administration of a foreign protein, operation on the sympathetic nerves was not indicated. These deductions were based on postoperative results obtained during the investigative study since it was noted that the increases in temperature observed before operation could be reproduced by sympathetic ganglionectomy and trunk resection. This result indicated that the actual flow of blood to the extremity had been increased by the operation. Utilizing this method of selection cases of thromboangiitis obliterans, with vasospasm of the collaterals, acral scleroderma, and atrophic arthritis, have thus been treated by the neurosurgical staff members of The Mayo Clinic.

Wade, and Wade and Royle in 1927 advocated ramisection for congenital megacolon. Their technic, slightly modified, was employed with complete success in three cases by Judd and the author, and subsequently was modified again and employed with success by Rankin and Learmonth. In 1930 Learmonth developed a surgical procedure for sectioning the presacral nerve in selected cases of incontinence of urine and trophic lesions of the bladder. C. H. Mayo and Devine have suggested and carried out sections of nerves to the stomach and pylorus for duodenal ulcer and pylorospasm, and Pieri has sectioned splanchnic nerves for gastric disorders.

RAYNAUD'S DISEASE

Raynaud's contributions, in 1862 and 1874, demonstrated that gangrene could develop in the digits without occlusion or demonstrable organic disease of the principal arteries. Bernard Schrader, in 1629, described a symmetric, recurring form of gangrene in the extremities of a young girl. The disease was not considered to be a vasomotor phenomenon until Raynaud called attention to the local asphyxia and cyanosis which preceded gangrene. Two schools of thought prevail concerning the underlying causes of Raynaud's disease. One holds that phenomena of vasomotor spasm involve small arteries, arterioles, and probably capillaries and venules; that the vasoconstrictor impulses are of central origin; and that the local responses to heat and cold are normal reflexes carried by vasomotor fibers, and are imposed on arteries and arterioles, producing pathologic states of contraction. The other school, the chief exponents of which are Krogh, and Lewis¹⁷ in collaboration with Kerr, holds that the defective circulation is due to fault of the digital arteries and vessels of smaller caliber, without

spasm of the veins, and that the phenomena are produced by cool temperatures and are relieved by heat. Lewis stated that these phenomena are the results of abnormality of the arteries, that this abnormality displays itself in hypersensitivity to reflexes initiated by relatively low temperature, and that the effects of cold are not produced through the intervention of the nervous system.

Etiology. The etiology is unknown. The influence of heredity, according to Monroe, may be made out in approximately 8 per cent of the cases. Persons of subnormal vasomotor type and of asthenic tendency are those who develop symptoms of true Raynaud's disease. The condition occurs more frequently in females than in males. Of Brown's patients 80 per cent were females and in Monroe's review of cases 62.6 per cent were females. The average age incidence according to Monroe's report was 30.9 years for both sexes.

Substantiating the argument that Raynaud's disease is primarily of central origin is the fact that Brown and I have seen it afflict patients who have lived in extremely hot regions, and have failed to see the symptoms subside when patients have moved from cold to hot climates. We have seen the changes in color of the skin take place in patients who have been subjected to severe emotional strain and in those who have become excited while in a hot room. We have also noted the failure of color changes to occur when patients have been exposed to cold and at the same time have been subjected to induced fever. The results of interruption of vasomotor

fibers constitute even more conclusive evidence that Raynaud's disease is of central origin and that the local changes in the extremities are controlled by vasomotor fibers. Horton and Craig have been able to produce these results experimentally. Following a successful operation the affected extremity becomes warm and pink and remains so permanently. The changes in color characteristic of asphyxia and cyanosis permanently disappear and cannot be brought on by exposure to cold or to emotional stimuli. Wagener has demonstrated that after cervicothoracic ganglionectomy and trunk resection in Raynaud's disease the retinal arteries and veins dilate from one and a third to one and a half their preoperative size. This dilatation is permanent. At the clinic we have had occasion to re-examine many of our patients, months and years subsequent to operation. In addition we have had the opportunity to measure and to compare the retinal arteries and veins of a man who underwent resection of the stellate ganglion on one side for anginoid pain eighteen years before, and we found that the arteries and veins on the side on which operation had been performed were one and a half times as large as those on the side on which operation had not been performed.

In partial support of Lewis' position may be cited the observation by Simpson, Brown, and Adson in a case of Raynaud's disease of the recurrence of cyanosis in the distal end of a digit on which there had been an ulcer, in spite of previous thorough operative interruption of the vasomotor fibers. This recurrence may have resulted from hypersensitivity of the arterioles

and capillaries, but I am more inclined to believe that it was due to faulty arterial circulation resulting from the capillary and arteriolar thrombosis, which gave rise to the primary ulcer. Recurrence of symptoms and of changes in color of the upper extremities were seen to occur when vasomotor fibers were missed, and considerable difficulty has been encountered in perfecting a surgical procedure that would thoroughly interrupt all of the vasomotor fibers to the arteries of the fingers and hand. The operative results following resection of the second, third, and fourth lumbar sympathetic ganglia, and of the intervening trunks have, however, always been successful. It is true that ulcers are much less common on the toes than they are on the finger tips; the toes are exposed less than the fingers to environmental temperature. It is apparent, however, that the surgical results depend directly on the thoroughness of the operation. This can be determined by the sweating test, since the sympathetic fibers to the sweat glands and pilomotor muscles are sectioned with the vasomotor fibers; they are closely associated, and cannot be separated at the time of operation. In the sweating test, dry heat must be employed and not pilocarpine, for pilocarpine is capable of stimulating the sweat glands directly and will produce secretions independent of the sympathetic innervation.

Pathologic Physiology. The underlying disturbances which produce the changes in color are easily studied by microscopy of the capillaries of the nailfold, and have been described by Muller, Parrisius, and Brown.¹⁴ In

the stage of pallor few capillaries are visible, filling of the loops with blood is incomplete, and the capillaries have a segmented or broken appearance. The blood contained in the capillaries is static²⁹; blood is not observed entering the capillary loops from the arterioles. The collecting venules are usually invisible, or contain small amounts of blood. In the stage of cyanosis blood is admitted into the capillaries both from the arterioles and by retrograde flow from the venules. The blood enters the capillaries in the form of small segments. The capillaries become dilated, an increased number of them is visible, and the blood in the loops is stationary, or flow occurs only after long intermissions. There is gradual deoxidation of the capillary blood, with increasing cyanosis. The capillaries may become greatly distended and may lose their characteristic shape. The collecting venules become dilated. With recovery, whether it is spontaneous or is induced by increasing the local or environmental temperature, the arterioles open, the flow of blood in the capillary loops becomes rapid, and the color of the blood changes to bright red. The stage of rubor, then, is due to a large number of open capillaries and venules containing red oxygenated blood. Many of these vessels remain to some degree dilated.

A summary of these studies corroborates in a striking manner the clinical deductions which were made by Raynaud on this mechanism. As he surmised, there is, in the stage of pallor or syncope, spasm of the arterioles, capillaries, and venules, the degree of pallor depending on the completeness of the spasm. The stage of

cyanosis is due to partial relaxation of the venules, with retrograde flow of blood in the capillary loops. Concomitant opening of the arterioles has been observed also, but the relaxation is not complete enough to allow the resumption of the usual flow. All gradations in behavior are noted in different cases; this amply explains the variations in color observed in certain subjects. Areas of moderate cyanosis may appear on one finger, and on another deep cyanosis may remain, or, in one area of skin there may be recovery, with return to normal pink or rubor, and the surrounding skin may be cyanotic.

Prognosis and Course. The prognosis of Raynaud's disease is subject to wide variations. As far as is known, it is never in itself a cause of death. In our experience, death has been due to the consecutive or the subsequent development of an entirely different disease. In mild cases, with local syncope or mild grades of cyanosis of the digits, there may not be any change over a long period of years. Many patients have been observed who have had vasomotor disturbance for more than ten years and yet have not suffered actual pain, trophic lesions, or progression of the disturbances of color. The previous course of the malady is probably of importance in considering the prognosis. In mild cases, in which the condition has remained unchanged for two or three years, the prognosis is usually good, and reassurance may be the only advice necessary. More usually there has been gradual progression from the stage of syncope; more digits have become involved, perhaps the entire

hand; and the condition has advanced into the stage of cyanosis, or syncope has alternated with cyanosis. Then, after variable periods of time, there may be gradual transition into a condition of chronic cyanosis of the extremities. Intermittent recovery of the parts is now less complete, and when recovery does take place it is accompanied by excessive sensations of heat and by excessive redness. Sensitivity to environmental temperature becomes more acute and the paroxysms are induced by slight variations in temperature, even during the summer months. Pain, numbness, or dull aching during the period of syncope and cyanosis are the rule. Small, dry ulcers of the skin of the digits may appear. In this primary type of case the prognosis is not good from the standpoint of spontaneous cure. The condition usually persists, and although it does not progress to the point of serious gangrene, yet it constitutes real disability to the patient. In the rarer forms, in which gangrene supervenes early in the course of the disease, the prognosis is most grave from the standpoint of preservation of the digits. In considering the prognosis, the important factor is the rate of progression of the disease in the first two or three years. Brown and I have observed that if at the end of this period trophic changes have not appeared, usually they will not appear later; and that long periods of remission may occur without known cause. This substantiates the argument that the disease is of central rather than of peripheral origin, and that its manifestations depend on the sympathetic reserve and the emotional stress of the patient.

Symptoms. Wide experience with various forms of vascular disease of the extremities allows separation of the cases presenting vasomotor disturbances of the spastic type into four groups.

First, there is a fairly large group of so-called normal persons, predominantly females, who have cold moist and clammy hands and feet associated with such disturbances as a mild degree of pallor in symmetric single digits, the so-called dead finger, or slight cyanosis. These persons are frequently of the asthenic type and suffer easily from cold. The surface temperature of the extremities is subject to wide fluctuations, depending on variations in environmental temperature. Such manifestations do not constitute a disease, and the physician is rarely consulted unless the changes in color are striking. These subjects are classified by Muller as having a "vasomotor constitution". At the clinic, we have designated them as suffering from subnormal vasomotor states.

Second, there are gradations from these so-called normal states to those in which the disturbances in color in the extremities are more profound, frequently paroxysmal, and occur even when the environmental temperature is not so low. Attacks of pallor may be followed in a period of months by more or less chronic states of cyanosis; or pallor and cyanosis may alternate for some time. The signs and symptoms are of sufficient intensity for the patient to seek advice from the physician. The symptoms usually consist of numbness and occasionally partial anesthesia during the period of local asphyxia, and of extreme coldness

during the stage of syncope. Dull aching distress is present during the periods of both syncope and cyanosis. With high environmental temperature, the hands become excessively warm and red, accompanied by sensations of burning.

Third, there is another group of persons who have further aggravation of the disturbance. The attacks of pallor become more intense and more painful, or a condition of chronic cyanosis or asphyxia supervenes; temporary recovery is much more difficult to effect. The changes in color are induced by emotional stimuli and by the least change in temperature. The hands and feet frequently become swollen and puffy. Trophic disturbances then appear, consisting of minute regions of gangrene in the tips of the digits, with symmetric distribution.

The fourth group consists of the more severe, but much rarer, type of case in which, without a prolonged antecedent history of vasomotor disturbance, gangrene may develop in the distal portions, rather than in the tips, of symmetric digits. Pain may be a marked feature.

All of these groups fulfill the criteria laid down by Raynaud; namely, symmetry of the disturbance, intermittency or paroxysmal nature of the disturbance, and pulsations in the arteries of the affected part. The groups seem to represent different degrees of the same underlying fault of the vasomotor mechanism, justifying the belief that the condition is a "vasomotor neurosis of the spastic type", and that the term Raynaud's disease should be reserved for the type of case included in the second, third, and fourth

groups. The cases in the first two groups probably represent an exaggeration of the vasomotor changes which affect the normal subject on exposure to cold. There is in the peripheral regions a transitory phase of pallor and of cyanosis; and with exposure to increased local or environmental temperature, redness and increased surface temperature result.

Clinical Considerations. The real problem is to select suitable cases for operation and to decide when operation is indicated. It is obvious that dilatation of an arteriosclerotic or occluded artery cannot be produced, and that surgical intervention is useless unless there is positive evidence that the disease has resulted from an inadequate supply of blood induced by vasospasm. The vasospastic phenomena may be intermittent or continuous. If they are intermittent and mild, disturbing symptoms or trophic changes do not occur, since complete recovery takes place between the attacks of vasomotor spasm.

Vasomotor Index. In a search for some means to determine the flow of blood to an extremity the capillaries were examined, and elimination of heat and surface temperature were measured. These procedures do not estimate exactly the volume of blood, but give relative estimates. One can observe the number of capillary loops to a given field and can determine the rate of flow of the corpuscles; and one can also measure the elimination of heat and the temperature of the skin, both of which are dependent on the flow of blood. By the Stewart-Kegerreis calorimeter the radiation of heat before and after operation could be determined, but it was not until Brown suggested recording the temperature of the skin before fever had been induced, and during its course, that there was any accurate knowledge concerning vasospasm. The electrodes of the elec-

trothermocouple are fastened to the various portions of the fingers, toes, hands, feet, and body, in preparation for readings of surface temperature. First, readings are recorded of the temperature of the room, and of the mouth and surface of the skin. Thus, corrections can be made for the environmental temperature, and the temperature of the mouth and skin can be compared with the corresponding temperatures of a normal person, and with the readings taken during the height of fever. The fever is produced by administering, intravenously, a foreign protein, for example, 5,000,000 to 75,000,000 dead bacilli in triple typhoid vaccine. The dose depends on the weight and sex of the patient. Hourly readings are made until the maximal rise of fever has been obtained. These readings are compared with the initial temperatures, to determine the ratios of increased temperature. General, regional, and spinal anesthesia produce vasodilator effects and can be employed instead of the administration of protein.

In studying the temperature of a normal person, it will be observed that the temperature of the mouth may have increased as much as an average of 2°C., whereas the temperature of the skin over the digits will have increased 4° to 6°C., or two to three times more than the mouth temperature, indicating that the peripheral arteries have been opened by inhibition of the vasomotor center and that more blood has been permitted to flow to the periphery. In cases of vasospastic disorder, the difference in temperatures is still greater, since the initial surface temperature of the digits is lower than that of a normal subject exposed to the same room temperature. In cases of general arterial sclerosis there may be little, if any, difference in the skin temperatures before and after administration of the foreign protein, indicating that the vessels are incapable of relaxing to allow increase of the flow of blood to the periphery. In cases of thromboangiitis obliterans it is possible to determine whether or not there exists an element of vasomotor spasm of the collateral vessels and unoccluded arteries; and it is possible, also, to determine, by individual readings, the condition of each digit. Therefore, the test serves as an index; and unless the rise

in temperature of the skin of the digits is two or more times greater than the rise of the oral temperature, the condition is considered inoperable. The test also permits determination of the degree of collateral circulation in different portions of the same digit.

Surgical Treatment. When medical treatment fails, surgical procedures have been instituted with the purpose of relieving vasomotor spasm. It has been proved that vasodilatation results from section of vasoconstrictor fibers, that the increase in temperature of the skin from injection of foreign protein can be reproduced by sympathetic ganglionectomy and trunk resection, and that the increased flow of blood in terms of increased elimination of heat continues and does not recede to the level at which it was before operation. Following interruption of all vasoconstrictor fibers, the pain disappears, swelling subsides, ulcers heal, nails grow, the characteristic changes in color disappear, arterial pulsations increase, and the skin appears normal, pale pink, and distinctly warmer and drier. The capillaries are found to be smaller in diameter than they were in the cyanotic phase but the stream of corpuscles is seen to flow much faster.

The surgical procedure which I have employed in interrupting the vasomotor fibers to the arteries of the lower extremities consists of an abdominal transperitoneal approach to the lumbar ganglia, and resection of the second, third, and fourth lumbar ganglia and the intervening trunks. The thorough interruption of the vasomotor fibers is thereby ensured. In this procedure, sympathetic trunks which give rise to the lateral branches of the presacral

nerves are severed; but inasmuch as clinical symptoms referable to the bladder or rectum do not develop from their inclusion, I see in this no contraindication. My purpose is to make sure that not only the lumbar rami are divided but also such truncal fibers and stray rami as might reënter the sacral nerves. In some instances the operation also serves as a treatment for constipation, since presacral fibers contribute to the innervation of the internal sphincters and to inhibition of the lower part of the large bowel and of the rectum. The sectioning of these presacral fibers has also reduced the inhibition of the detrusor muscles of the bladder, and has relaxed the internal sphincters, but since other presacral fibers remain undivided, symptoms are not manifest.

The problem of thoroughly interrupting all of the vasomotor fibers to the arteries of the upper extremities has been much more difficult to solve than that of interrupting the vasomotor fibers to the arteries of the lower extremities. The anatomic arrangement of the cervicothoracic ganglion is not constant. According to Kuntz⁴⁰ and the author's experience, this ganglion has been found to be fused in only 40 to 50 per cent of cases. Kuntz⁴⁰ has also demonstrated that postganglionic fibers may leave the thoracic trunk and ganglia as low as the second thoracic ganglion, and may pass directly to the lower trunk of the brachial plexus, without entering the so-called stellate ganglion. The anatomic arrangement, I believe, has been responsible for the partial successes and the failures in attempts to inter-

rupt all of the vasomotor fibers by the anterior-superior approaches to the cervicothoracic ganglion.^{18,21} The posterior approach, through the second rib, resulted in experiences similar to those noted in the superior-anterior approach^{65,66} except that the lower cervical ganglion was occasionally overlooked when it was not fused with the first thoracic, whereas in the anterior approach the first thoracic and the rami from the second thoracic ganglia were missed.

In the light of these experiences, I am employing a technic which consists of entering the mediastinum posteriorly through the first rib, an approach which gives exposure of the lower cervical and the first thoracic ganglia and allows of their resection.² Occasionally I am able to remove the second thoracic ganglion through the same operative field, but if it happens to lie low in the thoracic cavity, I proceed with thorough ramisection of the lower cervical and first thoracic nerves,

in addition to dividing all stray rami which may pass mesially to the thoracic trunk and accessory intercostal arteries. These measures insure against the entrance of stray postganglionic fibers into the brachial plexus. This procedure has been extremely satisfactory, but even yet an occasional fiber is overlooked and it may become necessary to follow this operation with further ramisection of the brachial plexus.

Results. In order to evaluate the results of sympathectomy in the treatment of Raynaud's disease in its various degrees of severity, cases have been classified in three groups. In the first group the cases are uncomplicated and the patients complain of asphyxia and cyanosis associated with paresthesia. In the second group are more advanced cases of active ulceration. In the third group are the most advanced cases in which ulcer or gangrene is associated with marked evidence of scleroderma and arthritis.

TABLE I
RAYNAUD'S DISEASE*

	CASES	AGE, YEARS	MALE	FEMALE	AVERAGE DURATION OF SYMPTOMS, MONTHS	AVERAGE DURATION OF SYMPTOMS SINCE SYMPATHECTOMY, MONTHS	CERVICOTHORACIC SYMPATHECTOMY	LUMBAR SYMPATHECTOMY
Group 1 (uncomplicated)	16	33.6	1	15	58.6	34.0	11	5
Group 2 (with ulcers)	6	25.7	0	6	71.0	40.7	3	3
Group 3 (with ulcers or gangrene with scleroderma and arthritis)	32	33.0	3	29	79.0	25.7	25	7
Total	54	30.7	4	50	69.5	33.2	39	15

*Illustrates the incidence of Raynaud's disease, sexes, average age, duration of disease previous to sympathectomy, the relation of the involvement to the upper and lower extremities, and the number of operations performed.

TABLE II
RAYNAUD'S DISEASE*

CERVICOTHORACIC SYMPATHECTOMY	CASES	AVERAGE RELIEF OF COLOR CHANGES, PER CENT	AVERAGE RELIEF OF PAIN, PER CENT	AVERAGE HEALING OF ULCERS, PER CENT	RECURRENT SIGNS	INCOMPLETE SYMPATHECTOMY
Group 1 (uncomplicated)	11	85	85	No ulcers	None	None
Group 2 (with ulcers)	3	60	60	100	1	1
Group 3 (with ulcers or gangrene with scleroderma and arthritis)	25	85	75	85	4	4
Total	39					

LUMBAR SYMPATHECTOMY	CASES	AVERAGE RELIEF OF COLOR CHANGES, PER CENT	AVERAGE RELIEF OF PAIN, PER CENT	AVERAGE HEALING OF ULCERS, PER CENT	RECURRENT SIGNS	INCOMPLETE SYMPATHECTOMY
Group 1 (uncomplicated)	5	100	100	100	None	None
Group 2 (with ulcers)	3	100	100	100	None	None
Group 3 (with ulcers or gangrene with scleroderma and arthritis)	7	90	90	90	None	None
Total	15					

*Illustrates the results accompanied by either cervicothoracic or lumbar ganglionectomy and trunk resection.

A review of tables 1 and 2 will show that the disease affects the upper extremities more often than the lower, and that the results from lumbar sympathectomy are better than those from cervicothoracic sympathectomy. The incomplete results in the fingers are apparently due to failures to include all of the vasomotor fibers when using the second rib approach, or to the advanced stage of the disease which has produced permanent changes in the peripheral circulation that do not permit vasodilatation of the arterioles or return to normal of the tremendously dilated capillaries.

The postoperative sequelae of these surgical procedures result in dryness of the skin, which can be relieved by application of lanolin and cocoa butter.

The Horner's syndrome of apparent enophthalmus, contracted pupils, and lagging of the lids due to relaxation of the musculus tarsalis is not a serious disfigurement if it is bilateral, nor does it interfere seriously with vision at night. Resection of the upper portion of the thoracic sympathetic trunk, and of the corresponding ganglia, does not materially alter acceleration of the heart, and none of the patients who have been subjected to the procedure has complained of cardiac symptoms after operation.

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans^{5,11,12} is characterized by vascular thrombosis of inflammatory causation, occurring in both arteries and veins but not at

the same levels in each. Arterial thrombosis usually occurs in the main peripheral arterial channels such as the dorsalis pedis, posterior tibial, radial and ulnar arteries. In the more severe cases, the arterial thrombosis ascends to include the popliteal and femoral arteries, and it may occur in the brachial arteries. Venous thrombosis is more of the recurring type, and may appear in any region of the foot, leg, thigh, or arm. Arterial thrombosis is likely to affect the arteries of one leg more than those of the other. But since the lesion has a tendency to progress and to spread, it may affect the opposite extremity, or the upper extremity, months or years after the onset. It has also been observed that when occlusion of the principal arteries of one extremity is present, the arteries of the other extremity, although still patent, may show diminished pulsation.

The disease has a predilection for young, asthenic males, but it does afflict robust males. It has been seen to occur in young, asthenic females. The vessels of two young females each of whom gave an antecedent history of having had symptoms simulating Raynaud's disease in all extremities, with accompanying sclerodermic and arthritic changes, were found to be thrombosed.

Symptoms. The initial symptoms usually consist of intermittent claudication on exertion in the muscles of the lower parts of the legs, but as the disease progresses pain is present even while the patient is at rest, and changes in color appear. The usual colors are those of rubor and cyanosis. They are

accompanied by the signs of passive congestion, of swelling, of localized phlebitis and of occluded arteries. The changes in color are more prominent when the extremity is held in a dependent position, and will disappear when the extremity is elevated. The degree of collateral circulation can be determined clinically by the time that is required for the color to return when the extremity is placed in a horizontal position. Ulcers and gangrene appear in the advanced stages of the disease.

Selection of Patients for Sympathetic Ganglionectomy and Trunk Resection. The rationale of carrying out lumbar ganglionectomy and trunk resection in cases of occlusive disease of the arteries affecting the extremities is based on the following clinical and physiologic observations: In many cases of thromboangiitis obliterans with closure of the main arteries, there are varying degrees of vasospastic disturbance. The changes in color due to lowered environmental temperature are in some cases so striking as to lead to an erroneous diagnosis of Raynaud's disease. This clinical observation suggests the conclusion that in some cases the collateral vessels, which maintain the circulation of the extremities, are subject to excessive vasospastic reactions. This is easily understood if the pathologic changes which occur in this disease are recalled; namely, marked inflammatory reaction in all coats of the arteries, especially in the adventitia or perivascular structures, and cellular thrombosis occluding segments of variable length. Further evidence of considerable vasomo-

tor spasm is obtained from the calorimetric and thermometric studies carried out on the extremities of these patients. The rate of elimination of heat, as determined in the hand or the foot calorimeter, and as measured in small calories eliminated for each unit of surface area for each unit of time, is subject to variations similar to, but less in degree than, those observed in normal subjects or in subjects with functional vasospastic disturbances. It may be assumed, therefore, that the diminished blood supply in some cases of thromboangiitis obliterans has a twofold basis; namely, occlusion of the main arterial channels, and superimposed vasoconstriction of the collateral circulation.

The medical treatment consists of rest in bed, application of dry heat, the use of contrast baths, and intravenous injection of protein. This is the treatment that should be employed in early and mild cases. The surgical treatment, until recently, has consisted of amputation, but in view of experience in the treatment of vasospastic disorders, such as Raynaud's disease, by sympathetic ganglionectomy and trunk resection, selected patients of this group have been subjected to similar operations. In our earlier experiences, before the introduction of the studies on induced fever, Brown and the author were compelled to operate without any particular method for the selection of patients, and had to judge from the results in previous cases whether or not a patient for whom the operation was contemplated would prove suitable. But with the advent of studies of cutaneous temperature, bet-

ter selection has been made possible. The same criteria have been employed as those adopted in the selection of cases of Raynaud's disease. However, selection should not be based on this method only, for it is unwise to operate on a patient during the period of extending arterial thrombosis; the danger is that the thrombosis may ascend to include the femoral artery and may result in gangrene in spite of the operation on the sympathetic system. Those patients who present themselves with acute processes are placed in bed, under medical treatment, until the lesion has become quiescent. This may require from three to six weeks. Patients with trophic ulcers, or gangrenous digits, are likewise treated medically, including administration of protein, until demarcation between healthy and diseased tissue appears and until healing of the ulcer begins; then operation is instituted. Occasionally it is wise to resect the thrombosed veins to hasten the convalescence.

Results. The results of sympathetic ganglionectomy in cases of thromboangiitis obliterans in properly selected cases are just as striking as those in cases of Raynaud's disease. The pain subsides, swelling disappears, and the ulcers heal with remarkable rapidity. Following the operation, spontaneous amputation of the gangrenous digits usually occurs at a level much lower than that at which surgical amputation would have been performed. The vasodilation and the improved circulation materially reduce the incidence of extending arterial thrombosis of the affected extremity, and they also reduce the incidence of its occurrence

in the opposite extremity. Intermittent claudication completely disappears in some cases, whereas in others it is only diminished. Pain disappears either entirely or when the part is at rest. The effect of interruption of vasomotor fibers to unoccluded and collateral arteries in thromboangiitis obliterans, is therefore to decrease the incidence of extension of thrombosis, to conserve extremities, to remove or lessen pain, to hasten the healing of ulcers, and to rehabilitate the patient for service within a period of months. The older type of treatment consisted of amputation, and maimed patients were the result.

In a carefully controlled series of 240 cases, 150 patients were treated medically and sympathectomy was performed on ninety. Brown and his collaborators have demonstrated repeatedly that preoperative increase in skin temperature from vaccine therapy has been reproduced and maintained by ganglionectomy and trunk resection, which proves that vasomotor spasm of the collateral vessels has been removed and that the circulation has been increased.

In reviewing the statistics of these cases it was observed that in 60 per cent of the cases the disease was confined to the lower extremities, and in only 2 per cent was it limited to the upper extremities. In 38 per cent both upper and lower extremities were involved. In 2 per cent massive gangrene was present, in 31 per cent gangrenous digits, in 36 per cent trophic ulcers, and in 31 per cent painful or swollen extremities. Ninety per cent of the patients complained of intermittent claudication, and 74 per cent

complained of rest pain. It was also observed in 98 per cent of these cases that when one extremity presented evidence of disease the corresponding extremity either showed or later developed occlusive arterial lesions with vasomotor spasm. It is this fact which has led the writer to perform bilateral sympathetic ganglionectomy.

The comparative results of treatment revealed that without adequate medical treatment the incidence of amputation was 25 per cent; with medical treatment it was reduced to 14 per cent, and with sympathectomy to 5 per cent. There were three deaths in the medical group and five in the surgical group. Fifty-six per cent of the patients treated medically were markedly improved, the remainder were subject to active recurrences. Eighty-three per cent of the patients treated surgically returned to gainful occupations with a cessation of the process in the less affected extremity.

SCLERODERMA

Adson, O'Leary and Brown, in 1929, stated that a third of the patients who consult a dermatologist for scleroderma give a history of vasospastic phenomena simulating Raynaud's disease. Scleroderma also may accompany thromboangiitis obliterans and certain types of arthritis. The vascular spasm in scleroderma is more or less continuous, and produces a constant reduction of the supply of blood to the extremities.¹⁷ Since the spasm and cyanosis can be temporarily relieved by application of heat, by the use of general, spinal, and regional anesthesia and by the administration of vaccine, this condition was studied in a

manner similar to that in which Raynaud's disease was studied. The changes in scleroderma simulate those that arise from a plaster cast that is too tight; namely, cyanosis, swelling, pain, atrophy, contracture, deformities, and disuse. The type of scleroderma under discussion differs from the amorphous type in that the disease affects chiefly the skin over the hands, forearms, face, neck, and scalp. The atrophy and contracting processes of the skin are associated with similar processes in the underlying structures, and it is not unusual for a patient to complain of weakness, inability to use muscles, and inability to open the mouth or to protrude the tongue. Arthritic changes often become manifest in the fingers; this condition is referred to as sclerodactylia. The changes associated with scleroderma are more pronounced in the skin of the uncovered parts, such as the hands, forearms, face, and neck, than they are in the covered parts, which suggests that reflex stimuli of cold accentuate existing vasomotor spasm. The fact that underlying tissues are subjected to atrophic changes suggests that vasospasm is not confined to the vessels of the skin, but that it interferes also with the circulation of all tissues.

Care should be exercised in selecting suitable cases, since the hide-binding process of scleroderma strangulates and destroys capillaries and arterioles which naturally cannot be opened by a vasodilating procedure. The vasomotor index again serves its purpose in the selection of operable cases. The postoperative results are dependent on the stage of the disease. The vascular phenomenon is corrected, as

in Raynaud's disease, and rehabilitation of skin and adjacent tissues will take place after operation if vasomotor spasm was present, and not too many capillaries and arterioles had been destroyed. If it is not possible to demonstrate the desired increase in surface temperature by administration of protein, little is to be expected from operation. Ankylosed joints are not made flexible by sympathetic ganglionectomy and trunk resection. It is wiser to choose the earlier cases for operation; improvement is more likely to occur in these cases than in advanced cases in which deformity has taken place.

Results. The cases were divided into three groups and classified on the basis of the relationship of the vasospastic phenomena to the development of the disease. In the first group were cases of primary scleroderma with vasomotor phenomena developing late in the disease. In the second group were cases in which scleroderma and vasomotor disturbances developed simultaneously. In the third group vasomotor disturbances preceded the development of scleroderma.

In the first group the vasomotor phenomena were improved, the skin temperature was increased, the skin became more flexible, and ulcers healed, but the results still were not as good as those observed in the third group. The outstanding accomplishment was the checking of the disease with an average improvement of 10 per cent.

In the second group the results were similar to those in the first group, but with a considerable restoration of function in addition and with an average improvement of 25 per cent.

In the third group the degree of recovery following lumbar sympathectomy averaged 85 per cent, whereas following cervicothoracic sympathectomy it averaged 45 per cent. In this group the skin not only became pink, warm, soft, and elastic but the muscles again became fusiform and flexible with a resultant improvement in strength. Patients who had been unable to open their mouths or to protrude their tongues were again able to masticate their food as formerly. The skin still remained very thick and bruised easily; ankylosed joints were unchanged.

CHRONIC ARTHRITIS

Because of the satisfactory results of lumbar sympathetic ganglionectomy and trunk resection for Raynaud's disease affecting the lower extremities, Rowntree suggested that the procedure be tried in a case of polyarthritis with vasospastic phenomena in which the condition was becoming progressively worse under medical treatment. The result was satisfactory, and since then numerous cases have been reported. However, the surgical procedure is limited to young persons who complain of cold, wet, pale, clammy skin and painful, swollen, tender joints with atrophy and contractures of the muscles. The procedure is of greatest value in the treatment of arthritic processes in the hands, wrists, feet, and ankles; it is less effective in arthritic lesions of the elbows, shoulders, knees, and cervical portion of the spinal column; it offers scarcely any relief in cases of lesions of the thoracic and lumbar portions of the spine.

Results. Immediately following operation, the skin over the extremities

becomes warm, pink, and dry giving evidence that the vasomotor fibers and those leading to the sweat glands have been interrupted. For five or six days the skin remains flushed; then it subsides to normal color, but if examination is made of the capillary loops after that period, and if their condition is compared with that before operation, it will be observed that the flow of blood, as indicated by movement of the corpuscles, has been distinctly increased. The pain and swelling become gradually less, and continue to decrease while the patient is in bed at rest; on movement of the joints or use of the extremity, the symptoms may temporarily reappear but subside again gradually. Very often, patients overdo during their convalescence because they feel so comfortable when at rest, and they are therefore prone to become discouraged in the first six months following operation. To obviate this feature, Rowntree urged graduated light exercise and physiotherapy, so as to avoid undue trauma during this period of restoration. Some patients do not experience as much discomfort as others and progress slowly from the onset. The usual course, however, is for a patient to experience marked relief immediately following operation, then for pain and soreness partially to return for three or four months, and finally for gradual and permanent recovery from pain, tenderness, and swelling of the extremities to supervene. The mobility and the return of function continue parallel with the reduction in pain and swelling and the development of muscular function.

Tables III and IV contain data on

TABLE III
CHRONIC ARTHRITIS: TYPES OF CASES IN WHICH OPERATION WAS PERFORMED

GROUP	CASES*	GENERAL RESULTS	AVERAGE			
			AGE AT ONSET, YEARS	DURATION OF SYMPTOMS, MONTHS	VASCULAR INDEX (G. E. BROWN)	INCREASE IN CUTANEOUS TEMPERATURE, DEGREES C.
1	6	Failure	28	92	6.9	9.0
2	11	Slight (30 per cent) improvement	29	76	4.4	7.0
3	20	Marked (70 per cent) improvement	21	58	4.9	7.6

*In four of the forty-one cases studied, operations were performed too recently to be included in the table; the patients were still in the hospital at the time this paper was written.

the types of cases in which operation was performed, and on the results obtained. Group 1 represents the cases in which the disease was most advanced and in which there were numerous ankylosed joints. In such cases sympathectomy is of no value. Group 2 represents the border-line cases, in which sympathetic ganglionectomy and trunk resection may be justified in the hope of reducing the pain and of checking the disease. Group 3 represents the cases in which sympathetic ganglionectomy and trunk resection has produced satisfactory results and in which it is indicated.³²

Hench, Henderson, Rowntree and the author believe that operation on the sympathetic system is not indicated in any arthritic condition until thorough investigation and intensive medical treatment have been employed; but if the lesion is progressive, that is, if it is inactive only when some form of heat which improves the circulation locally is being administered, operation is advisable. The studies to be made, and the indications to be ob-

served are similar to those requisite before operative treatment of any vasospastic disorder.

CONGENITAL MEGACOLON

The term "congenital megacolon" has come to mean a condition of dilated, hypertrophied colon resulting from interference with the normal peristaltic function, but it does not indicate whether the condition is of mechanical or of neurogenic origin. Since the advanced degrees of the mechanical type require different operative procedures from advanced degrees of the neurogenic type, a more accurate classification is necessary. Acute obstructions of the large bowel result in dilatation and distention, whereas chronic obstructions produce compensatory hypertrophy with dilatation. Bands, adhesions, chronic volvulus, and tumors are responsible for mechanical blockage. Neurogenic lesions produce symptoms similar to those of mechanical origin, but the condition is usually discovered in youth or is present at birth. Neurogenic lesions are

TABLE IV
RESULTS OF SYMPATHETIC GANGLIONECTOMY AND TRUNK RESECTION FOR
CHRONIC ARTHRITIS (FAILURES OMITTED)

AVERAGE DEGREE OF :	GROUP 2* (11 CASES) SLIGHT IMPROVEMENT	GROUP 3** (10 CASES) MARKED IMPROVEMENT
General improvement, per cent	20 to 30	70
Relief of pain, per cent	34	75
Reduction in swelling, per cent	32	67
Increase in motion, per cent	17	64
Decrease in deformity, per cent	8	54
Improvement in function, per cent	7	70
Improvement in walking, per cent	11	70
Degree of ability to carry on regular work, per cent		74

*Arthritis progressed, in extremities for condition of which operation was not done, in five cases and remained stationary in three, and did not develop in three.

**Arthritis progressed, in extremities for condition of which operation was not done, in six cases, remained stationary in two, and improved in two.

characterized by chronic obstipation which can be temporarily relieved by enemas, purging and dilatation of the anus, especially if these measures are supplemented by the use of a diet without residue. The symptoms vary in degree, but they are not permanently relieved by medical treatment. General surgeons have resorted to colostomy and colectomy. The results have been variable and the mortality high. Wade, at the suggestion of Royle, performed ramisection and trunk resection in a case of megacolon of neurogenic origin. This was the first attempt to cure the condition by operation on the nervous system.

Anatomy and Physiology of the Rectum and Bladder. Gaskell has pointed out that there are three sphincter muscles which terminate the different regions of the primitive gut: (a) the ileocolic sphincter at the end of

the small intestine; (b) the internal anal sphincter at the end of the coprodeum; (c) the internal vesical sphincter and the urethral muscles at the end of the urodeum. The motor nerve cells for the ileocolic sphincter are situated in the superior mesenteric ganglion, while the motor nerve cells for the internal anal sphincter and the internal vesical sphincter are in the inferior mesenteric ganglion.^{25,42,24} The inhibitory nerves to the internal sphincter ani and to the internal sphincter of the bladder, according to Elliott, travel through the pelvic nerve as a part of the sacral outflow. The motor nerves to the musculature of the large intestine, according to Bayliss and Starling,^{12,13} and also Langley and Anderson,⁴² are likewise a part of the sacral outflow and travel through the pelvic nerve. Elliott has confirmed this by the injection of adrenalin which

causes no contraction whatever of any part of the large intestine with the exception of the internal sphincter ani.²³ The inhibition of the musculature of the large intestine is mediated through inhibitory nerves whose cells are situated in the inferior mesenteric ganglion²⁴; stimulation of the lumbar splanchnics, or of the hypogastric nerves, causes relaxation of the musculature of the colon.

Limitation of space prevents the quoting in full of the detailed description of the anatomy of the innervation of the anal and vesical sphincter and of the colon, which has been given by Learmonth. This author favors section of the presacral and inferior mesenteric nerve in megacolon of urogenic origin. His views are well represented in the following quotation.

"The colon is dilated, and the dilation is most marked in its distal part, sometimes reaching the internal sphincter of the anus. Although the muscular coat is hypertrophied, it is unable to transmit the content of the intestine. Even if, in our ignorance of its ultimate cause, we cannot attack the disease directly, we may still carry out flanking attacks in three directions: (1) we may attempt to diminish the dilation of the colon; (2) we may try to leave its motor nerves in less disputed control; and (3) we may attempt to relieve any opposition to the expulsion of the content of the bowel offered by the internal sphincter of the anus. If our anatomic and physiologic reasoning is correct, we can accomplish the first and the second objects by division of the inferior mesenteric nerves and the third by division of the presacral nerve.

"Next it must be inquired if these operations can be performed without endangering the functions of any viscera, by interrupting important efferent or afferent fibers. In particular, it is essential to safeguard the afferent fibers from the ampulla of the rectum, so that the mechanism for defecation may be set in motion when fecal matter enters that part of the bowel. In the dog, division of the inferior mesenteric nerves results only in increase in the tonus of the distal part of the colon, and in the patients on whom we performed this operation, the only discernible effect on the colon was the desired one. With regard to the presacral nerve, there is abundant evidence of its functions in man; it is an important afferent path for painful impulses, particularly from the female genitalia and from the bladder; it probably contains inhibitory fibers for the musculature of the bladder, but only rarely, after its section, is transient frequency of micturition observed; and it supplies motor fibers to the internal sphincter of the anus. The afferent fibers concerned in reflex defecation pass to the spinal cord largely if not entirely by way of the pelvic nerves and the second, third, and fourth sacral posterior roots; they are preserved in the suggested operation, which may be performed without fear of producing undesirable results."

Wade's clinical results have convinced him that section of the white ramus to the first lumbar ganglion, and of the medially directed fibers from the sympathetic trunk, together with section of the sympathetic trunk below the fourth lumbar ganglion on the left side, is sufficient. Judd and

the author, before the suggestion of Rankin and Learmonth, resected the second, third, and fourth ganglia and intervening trunks on both sides, in order to interrupt postganglionic fibers composing lateral branches of the presacral nerves, in addition to interrupting fibers passing from the second lumbar ganglion and fibers descending in the lumbar sympathetic trunk to communicate with the intermesenteric plexus, which supplies the inferior mesenteric nerve.

Results. Sympathectomy has been performed without a fatality in eight cases of Hirschsprung's disease of children and in two cases of acquired megacolon of young women. The patients have recovered from their symptoms. The colon has been reduced in size but has not returned to normal.

Since either procedure appears to have accomplished the desired result the ultimate choice of operation will be determined by comparison of cases. The operation of Rankin and Learmonth has the advantage of not interrupting vasomotor fibers to the extremities. That interruption of these fibers is not a serious disadvantage of ramisection, trunk resection, or ganglionectomy, is shown by the fact that patients with spastic paralysis or with vasomotor disturbance on whom such operations have been performed do not complain of excessive heat in their feet.

CORD BLADDER

Learmonth, and Learmonth and Braasch have shown that urinary retention resulting from spina bifida, tumor of the spinal cord, inflammatory lesions and injuries which interfere

with the parasympathetic innervation to the bladder through the second, third, and fourth sacral nerves, can be partially or totally relieved by section of the presacral sympathetic fibers. This is possible because these fibers represent the reciprocal innervation of the detrusor muscle and of the internal sphincter. Section of the presacral fibers reduces the inhibitory impulses to the muscle of the bladder and relaxes the internal sphincter. Also, Learmonth has shown that trophic lesions can be improved by the same operative procedure, since the vasomotor fibers are intermingled with those which carry inhibitory and contractile impulses. Painful sensations are partially reduced also by section of the presacral nerves, since afferent fibers are found in these nerves, although the largest afferent element from the bladder returns to the spinal cord by way of the hypogastric plexus and sacral nerves.

Results. The following résumé was prepared by Learmonth who has permitted me to include it in this paper. He states that at The Mayo Clinic sympathetic neurectomy has been undertaken in disturbance in vesical function in three types of cases:

1. *Paresis of the Musculature of the Bladder.* When a bladder is incapable of emptying completely as a result of injury to any portion of the parasympathetic pathway, it has seemed reasonable to suppose that the intact sympathetic contribution to vesical innervation provided too effective a brake for the decreased parasympathetic innervation, and that after sympathetic neurectomy the diminished activity of the evacuant set of nerves would be unhampered by this brake. Operation has been carried out in eight cases of this type, one of which has

been reported in detail elsewhere.⁴⁵ One patient in this series cannot be traced, and one failed to receive benefit. Of the remainder, two are considered cured (for periods of two years and one and a half years, respectively), and the expulsive power of the bladder of the other four patients has been materially improved; the amount of residual urine has been reduced from 200 or 300 c.c. to 20 or 30 c.c. It is necessary to warn men that after the operation, although they will be able to perform the sexual act and to experience a normal orgasm, ejaculation will not occur; no detectable alteration in reproductive function follows the operation on women. It has been found that after two or three weeks the internal sphincter of male subjects recovers a portion of its tonus, although the trigone, bereft of its motor nerve supply, remains flaccid. A small quantity of residual urine may persist as a trigonal pool; in these cases a channel is made from the pool to the posterior urethra by the operating cystoscope, and this operation has often enabled the bladder to expel its contents completely.

2. *Spasm of the Neck of the Bladder.* In two cases in which there was difficulty in starting the flow of urine, a diagnosis was made of spasm, or better, achalasia, of the internal vesical sphincter. In both cases, urologic and neurologic examinations were negative, and attempts had been made to rectify the condition by punch operations on the neck of the bladder. Because the sympathetic system provides motor nerves to the internal sphincter, it was thought that its overcontraction would be diminished by sympathetic neurectomy. The operation was immediately successful in both cases, and neither patient has had any subsequent difficulty in beginning or in completing the act of micturition.

3. *Inveterate Vesical Pain.* Since 1926, when Pieri first performed presacral neurectomy for the relief of vesical pain, a number of successful operations has been recorded. Pieri has devised a more complete procedure, which aims at interrupting all possible sympathetic paths from the bladder to the central nervous system; this he considered necessary, because one or two fine branches may connect the hypogastric

ganglia directly to the sacral paravertebral sympathetic ganglia. The complete operation interrupts impulses which, after reaching the hypogastric ganglia, might pass by fibers traversing the paravertebral chains either to the sacral nerves by way of the rami communicantes, and so to the spinal cord, or, after ascending in the paravertebral chain, by way of lumbar or thoracic rami communicantes to the spinal cord at a higher level.

Among the conditions in which this operation has been tested at The Mayo Clinic are interstitial cystitis, inoperable carcinoma of the bladder, chronic cystitis of unknown etiology, and the irritability of the bladder which may remain after nephrectomy for renal tuberculosis. The result has been satisfactory in six of eleven cases. There has not been any marked difference between the result after simple presacral neurectomy, and that after the more extensive operation. The relief from pain is due chiefly to mitigation of the spasmodic and uncoordinated contractions of the musculature.

SUMMARY

Sympathectomy has become a useful procedure. Physiologic data and clinical indications for operation are becoming gradually crystallized. Opinions may have to be altered and new ideas will arise, but the author feels confident that sympathectomy, in its various forms, is a surgical procedure that will continue as a means of treatment in conditions of dysfunction of blood vessels, smooth muscle, and glands.

It is obvious that progress in this field requires the coöperation of the anatomist, the physiologist, and the clinician and that it would be unwise for the surgeon to attempt operations on the sympathetic system unless he is thoroughly familiar with the anatomy of the fields concerned.

BIBLIOGRAPHY

- ¹ADSON, A. W.: Surgical relief of Raynaud's disease and other vascular disturbances by sympathetic ganglionectomy and perivascular neurectomy, *Ann. Clin. Med.*, 1926, v, 161-167.
- ²ADSON, A. W.: Cervicothoracic ganglionectomy, trunk resection, and ramisectomy by the posterior intrathoracic approach, *Am. Jr. Surg.*, 1931, xi, 227-232.
- ³ADSON, A. W., and BROWN, G. E.: Treatment of Raynaud's disease by lumbar ramisection and ganglionectomy and perivascular sympathetic neurectomy of the common iliacs, *Jr. Am. Med. Assoc.*, 1925, lxxxiv, 1908-1910.
- ⁴ADSON, A. W., and BROWN, G. E.: Raynaud's disease of the upper extremities; successful treatment by resection of sympathetic, cervicothoracic and second thoracic ganglia and intervening trunk, *Jr. Am. Med. Assoc.*, 1929, xcii, 444-449.
- ⁵ADSON, A. W., and BROWN, G. E.: The treatment of Raynaud's disease by resection of the upper thoracic and lumbar sympathetic ganglia and trunks, *Surg., Gynec., and Obst.*, 1929, xlviii, 577-603.
- ⁶ADSON, A. W., and HENDERSON, M. S.: Sympathetic ganglionectomy and trunk resection in arthritis: indications and results, *Jr. Bone and Joint Surg.*, 1932, xiv, 47-560.
- ⁷ADSON, A. W., O'LEARY, P. A., and BROWN, G. E.: Surgical treatment of vasospastic types of scleroderma by resection of sympathetic ganglia and trunks, *ANN. INT. MED.*, 1930, iv, 555-568.
- ⁸ADSON, A. W., and ROWNTREE, L. G.: Bilateral lumbar and thoracic sympathetic ganglionectomy and ramisectomy for polyarthritis of the lower and of the upper extremities, *Trans. Assoc. Am. Phys.*, 1929, xlv, 221-230.
- ⁹ADSON, A. W., and ROWNTREE, L. G.: Surgical indications for sympathetic ganglionectomy and trunk resection in the treatment of chronic arthritis, *Surg., Gynec., and Obst.*, 1930, 1, 204-215.
- ¹⁰AVENUE, H.: Effect of sympathectomy upon the pain of organic disease of arteries of the lower limbs and for obscure abdominal pain, *Trans. Am. Surg. Assoc.*, 1928, xlv, 179-189.
- ¹¹BARRON, M. E., and LINENTHAL, H.: Thromboangiitis obliterans: general distribution of the disease, *Arch. Surg.*, 1929, xix, 735-751.
- ¹²BAYLISS, W. M., and STARLING, E. H.: The movements and innervation of the small intestine, *Jr. Physiol.*, 1899, xxiv, 99-143.
- ¹³BAYLISS, W. M., and STARLING, E. H.: The movements and innervation of the small intestine, *Jr. Physiol.*, 1901, xxvi, 125-138.
- ¹⁴BROWN, G. E.: The skin capillaries in Raynaud's disease, *Arch. Int. Med.*, 1925, xxxv, 56-73.
- ¹⁵BROWN, G. E., and ADSON, A. W.: Calorimetric studies of the extremities following lumbar sympathetic ramisection and ganglionectomy, *Am. Jr. Med. Sci.*, 1925, clxx, 232-240.
- ¹⁶BROWN, G. E., and ADSON, A. W.: Physiologic effects of thoracic and of lumbar sympathetic ganglionectomy or section of trunk, *Arch. Neur. and Psych.*, 1929, xxii, 322-357.
- ¹⁷BROWN, G. E., O'LEARY, P. A., and ADSON, A. W.: Diagnostic and physiologic studies in certain forms of scleroderma, *ANN. INT. MED.*, 1930, iv, 531-554.
- ¹⁸BRÜNING, F.: Weitere Erfahrungen über den sympathicus, *Klin. Wehnschr.*, 1923, ii, 1872-1874.
- ¹⁹BUERGER, L.: Thromboangiitis obliterans: a study of the vascular lesions leading to pre-senile spontaneous gangrene, *Am. Jr. Med. Sci.*, 1908, cxxxvi, 567-580.
- ²⁰DAVIS, L., and KANAVEL, A. B.: Sympathectomy in Raynaud's disease, erythromelalgia, and other vascular diseases of the extremities, *Surg., Gynec., and Obst.*, 1926, xlii, 729-742.
- ²¹DAVIS, L., and KANAVEL, A. B.: The effect of sympathectomy on spastic paralysis of the extremities, *Jr. Am. Med. Assoc.*, 1926, lxxxvi, 1890-1893.
- ²²DÍEZ, J.: El tratamiento de las afecciones tróficas y gangrenosas de los miembros por la resección de las cadenas cervico-

- tóracica y lumbo-sacra del simpático, Prensa méd., Argentina, 1925, xii, 377-403.
- ²³ELLIOTT, T. R.: The action of adrenalin, Jr. Physiol., 1905, xxxii, 401-467.
- ²⁴ELLIOTT, T. R.: The innervation of the bladder and urethra, Jr. Physiol., 1907, xxxv, 367-445.
- ²⁵ELLIOTT, T. R., and SMITH, E. B.: Antiperistalsis and other muscular activities of the colon, Jr. Physiol., 1904, xxxi, 272-304.
- ²⁶FULTON, J. F.: Vasomotor and reflex sequelae of unilateral cervical and lumbar ramisectomy in a case of Raynaud's disease, with observations on tonus, Ann. Surg., 1928, lxxxviii, 827-841.
- ²⁷GASKELL, W. H.: Further researches on the vasomotor nerves of ordinary muscles, Jr. Physiol., 1878-1879, i, 262.
- ²⁸VON GAZA, W.: Die Resektion der paravertebralen Nerven und die isolierte Durchschneidung des Ramus communicans. Zugleich ein Beitrag zur Behandlung der vegetativen Neurosen innerer Organe, Arch. f. klin. Chir., 1924, cxxxiii, 479-500.
- ²⁹GREENE, C. W.: Personal communication to the author.
- ³⁰HARRIS, S., and HARRIS, R. G. S.: Renal sympathetic tonus and renal sympathectomy. (In press)
- ³¹HENCH, P. S., HENDERSON, M. S., ROWNTREE, L. G., and ADSON, A. W.: Treatment of chronic "infectious" arthritis by sympathetic ganglionectomy and trunk resection, Jr. Lab. and Clin. Med., 1930, xv, 1247-1256.
- ³²HENDERSON, M. S., and ADSON, A. W.: Sympathetic ganglionectomy and trunk resection in arthritis: indications and results, Jr. Bone and Joint Surg., 1932, xiv, 46-56.
- ³³HORTON, B. T., and CRAIG, W. McK.: Evidence shown in roentgenograms of changes in the vascular tree following experimental sympathetic ganglionectomy, Arch. Surg., 1930, xxi, 698-701.
- ³⁴JABOULAY: Quoted by LERICHE, R.: De l'élongation et de la section des nerfs perivasculaires dans certains syndromes douloureux d'origine artérielle et dans quelques troubles trophiques, Lyon chir., 1913, x, 379-392.
- ³⁵JONNESCO, T.: Traitement chirurgical de l'angine de poitrine par la résection du sympathique cervico-thoracique, Presse méd., 1921, xxix, 193.
- ³⁶JUDD, E. S., and ADSON, A. W.: Lumbar sympathetic ganglionectomy and ramisectomy for congenital idiopathic dilatation of the colon, Ann. Surg., 1928, lxxxviii, 479-498.
- ³⁷KEGERREIS, R.: Calorimetric studies of the extremities. II. Experimental apparatus and procedures, Jr. Clin. Invest., 1926, iii, 357-367.
- ³⁸KRAMER, J. G., and TODD, T. W.: The distribution of nerves to the arteries of the arm, with a discussion of the clinical value of results, Anat. Rec., 1914, viii, 243-255.
- ³⁹KROGH, A.: The anatomy and physiology of the capillaries, 1922, Yale University Press, New Haven.
- ⁴⁰KUNTZ, A.: Distribution of the sympathetic rami to the brachial plexus: its relation to sympathectomy affecting the upper extremity, Arch. Surg., 1927, xv, 871-877.
- ⁴¹KUNTZ, A.: The autonomic nervous system, 1929, Lea and Febiger, Philadelphia.
- ⁴²LANGLEY, J. N., and ANDERSON, H. K.: Note on regeneration of preganglionic fibres of the sympathetic, Jr. Physiol., 1895, xviii, 280-284.
- ⁴³LEARMONTH, J. R.: Neurosurgery in the treatment of diseases of the urinary bladder. III. The treatment of certain types of vesical paralysis, Jr. Urol., 1931, xxvi, 229-232.
- ⁴⁴LEARMONTH, J. R., and BRAASCH, W. F.: Resection of the presacral nerve in the treatment of cord bladder: preliminary report, Surg., Gynec., and Obst., 1930, li, 494-499.
- ⁴⁵LEARMONTH, J. R.: Neurosurgery in diseases of the urinary bladder, Am. Jr. Surg., 1932, xvi, 270-274.
- ⁴⁶LERICHE, R., and FONTAINE, R.: Chirurgie du sympathique, Rev. neur., 1929, i, 1046-1085.
- ⁴⁷LEWIS, T.: Experiments relating to the peripheral mechanism involved in symp-

- modic arrest of the circulation in the fingers, variety of Raynaud's disease, *Heart*, 1929, xv, 7-10.
- ⁴⁵MAYO, C. H.: The mechanism of abdominal pain, *Brit. Med. Jr.*, 1929, ii, 703-704.
- ⁴⁶MONRO, T. K.: Raynaud's disease, 1899, James Maclehose and Sons, Glasgow.
- ⁵⁰MOUNT, H. T. R.: Experimental study of the effects of stimulation and section of the vagal innervation to the bronchi and their possible relation to asthma, *Am. Jr. Med. Sci.*, 1929, clxxvii, 697-704.
- ⁵¹MULLER, G. P.: Surgical relations of the sympathetic nervous system, *Ann. Surg.*, 1923, lxxvii, 641-651.
- ⁵²ORBELI, Z. A.: Personal communication to the author.
- ⁵³PARRISIUS, W.: Kapillarstudien bei Vasoneurosen, *Deutsch. Ztschr. f. Nervenhe.*, 1921, lxxvii, 310-358.
- ⁵⁴PIERI, G.: La resezione dei nervi splancnici, *Ann. ital. d. chir.*, 1927, vi, 678-684.
- ⁵⁵PIERI, G.: La resezione dei nervi, *Ann. ital. d. chir.*, 1928, ix, 1-13.
- ⁵⁶PORRS, L. W.: The distribution of nerves to the arteries of the leg, *Anat. Anz.*, 1914, xlvii, 138-143.
- ⁵⁷RANKIN, F. W., and LEARMONTH, J. R.: Section of the sympathetic nerves of the distal part of the colon and the rectum in the treatment of Hirschsprung's disease and certain types of constipation, *Ann Surg.*, 1930, xcii, 710-720.
- ⁵⁸RAYNAUD, M.: On local asphyxia and symmetrical gangrene of the extremities, *Selected Monographs*, New Sydenham Society, London, 1888, vii-x, 1-150.
- ⁵⁹ROWNTREE, L. G., and ADSON, A. W.: Bilateral lumbar sympathetic neurectomy in the treatment of malignant hypertension: report of a case, *Jr. Am. Med. Assoc.*, 1925, lxxxv, 959-961.
- ⁶⁰ROWNTREE, L. G., and ADSON, A. W.: Polyarthritik: further studies on effects of sympathetic ganglionectomy and ramisection, *Jr. Am. Med. Assoc.*, 1929, xciii, 179-182.
- ⁶¹ROWNTREE, L. G., ADSON, A. W., and HENCH, P. S.: Preliminary results of resection of sympathetic ganglia and trunks in seventeen cases of chronic "infectious" arthritis, *ANN. INT. MED.*, 1930, iv, 447-454.
- ⁶²ROWNTREE, L. G., WALTERS, W., and CRAIG, W. McK.: Renal sympathectomy. (In press)
- ⁶³ROYLE, N. D.: The treatment of spastic paralysis by sympathetic ramisection, *Surg., Gynec., and Obst.*, 1924, xxxix, 701-720.
- ⁶⁴ROYLE, N. D.: A new operative procedure in the treatment of spastic paralysis, and its experimental basis, *Med. Jr. Australia*, 1924, i, 77-86.
- ⁶⁵ROYLE, N. D.: The surgical treatment of Raynaud's disease and similar conditions, *Trans. Australasia Med. Cong.*, 1927, ii, 341-343.
- ⁶⁶ROYLE, N. D.: Sympathetic trunksection; a new operation for Raynaud's disease and spastic paralysis of the upper limb, *Med. Jr. Australia*, 1928, ii, 436-439.
- ⁶⁷ROYLE, N. D.: Clinical results following operation of sympathetic ramisection, *Brit. Med. Jr.*, 1930, ii, 628-631.
- ⁶⁸SCHRADER, B.: Quoted by Raynaud.
- ⁶⁹SCRIMGER, F. A. C.: On the possibility of relieving abdominal pain by section of the sympathetic rami communicantes, *Can. Med. Assoc. Jr.*, 1929, xxii, 184-189.
- ⁷⁰SIMPSON, S. L., BROWN, G. E., and ADSON, A. W.: Raynaud's disease: evidence that it is a type of vasomotor neurosis, *Arch. Neur. and Psychiat.*, 1931, xxvi, 687-718.
- ⁷¹STEWART, G. N.: Studies on the circulation in man. I. The measurement of the blood flow in the hands, *Heart*, 1911-1912, iii, 33-84.
- ⁷²WADE, R. B.: Unpublished data.
- ⁷³WADE, R. B., and ROYLE, N. D.: Operative treatment of Hirschsprung's disease; a new method, *Med. Jr. Australia*, 1927, i, 137-141.
- ⁷⁴WAGENER, H. P.: Ocular changes following cervicothoracic sympathetic ganglionectomy, *Surg. Clin. N. Am.*, 1931, xi, 867-875.

Pathologic Differentiations in Bright's Disease* †

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ONE'S conception of a pathologic differentiation may vary greatly depending on the implications found in the term "pathology". For those to whom the word suggests "morbid anatomy" a pathologic differentiation would seem adequate when it has accurately described structural differences between disease processes. It is this manner of differentiation which has been applied in great detail to the renal lesion in Bright's disease by pathologists, for their differentiations in this condition have consisted mainly in contrasting inflammatory processes in the glomeruli with degenerative changes in the tubules or sclerotic lesions in the arteries. In this way various types of the disease have been established, and though such a method is perhaps the best available for purposes of classification, since it is based on that sound concept which recognizes the importance of structural change as the determining factor in disease, we must recognize the fact that, in such a form as has been used in the past, the method is woefully inadequate as a means of establishing any complete concept

of disease processes. This is so because such pathologic differentiation does not include within its scope an objective demonstration of both the structural and functional aspects of the abnormality.

Now it is obvious that what causes man to suffer is altered or arrested function, not the presence or absence of this or that mass of tissue cells. And so in his differentiations in Bright's disease the pathologist has been forced to supply for his structural abnormalities suitable functional significances. But in many instances, in fact in the great majority, his objective endeavor has ceased when he has completed only the first half of his differentiation, that is the demonstration of structural abnormality, and the second half which concerns the essential functional aspect of the damage, is supplied by recourse to a subjective process, namely his scientific imagination. Angiospasm is assumed to occur in a diseased arteriole, an inflamed glomerulus to be less competent as a filter. You can think of many analogous combinations of structural and functional damage, where the pathologist has suggested that tissues which appear different are acting differently, but it is the rare case indeed where he can give you any objective evidence that his assumption is correct. There

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always remains, therefore, the disturbing possibility that it is not the queer looking cell which is incompetent but rather the pathologist.

I would like to describe, therefore, a pathologic differentiation in which,

epithelium of the convoluted tubules and though this cell destruction varies in intensity in the various types of the disease it is always sufficient to require repair. Under the simplest conditions, such as in the degenerative lesions fol-

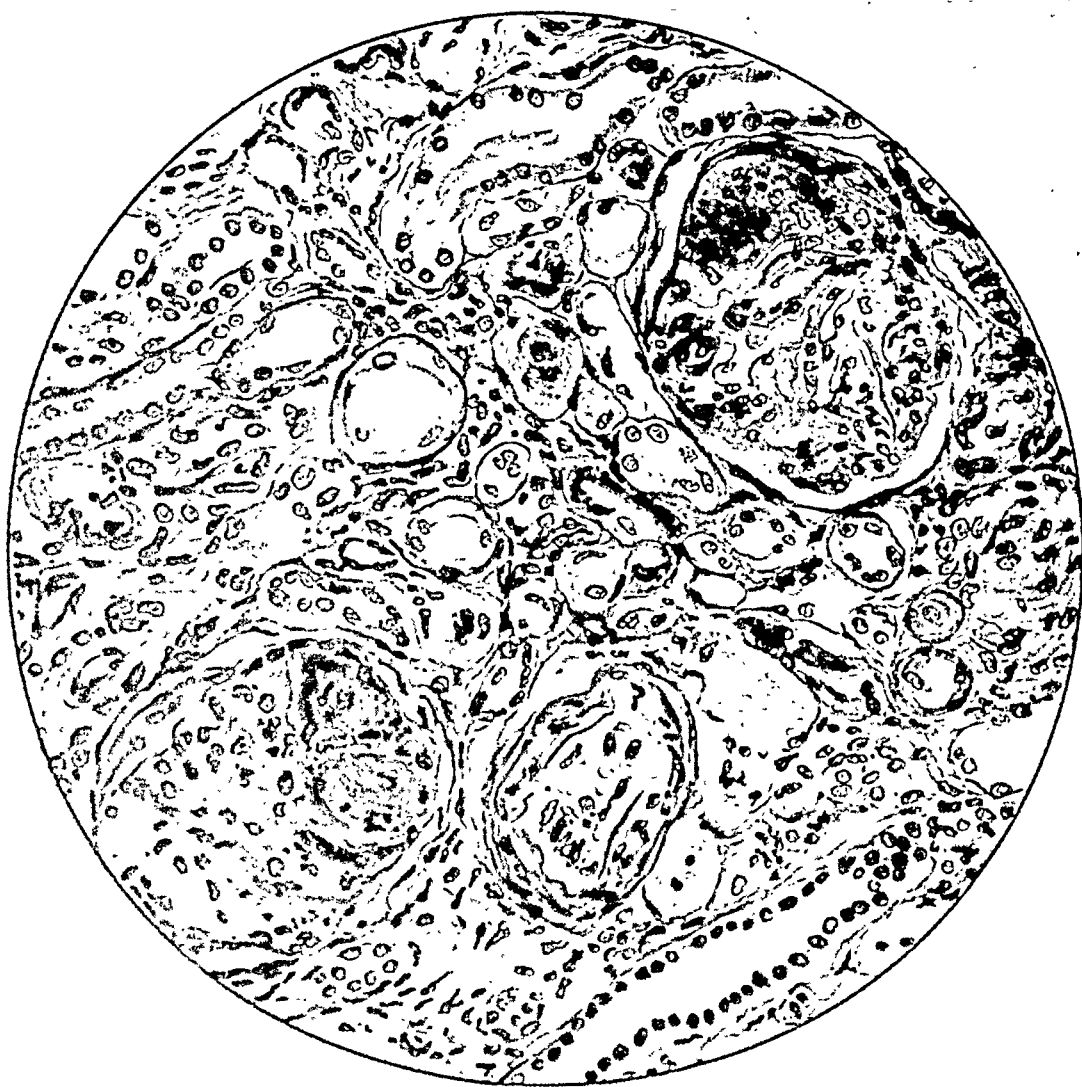


FIG. 1. Active stage of hemorrhagic Bright's disease. Hyaline thrombosis and necrosis with nuclear debris are seen in the glomerular tufts. The original epithelium of all the convoluted tubules is replaced by an atypical irregular lining of immature regenerated cells.

due to the simplicity of conditions, it is possible to complete this essential correlation of structural and functional abnormality. The general problem may be stated as follows.

In all forms of Bright's disease there occur regenerative changes in the

lowing corrosive sublimate, the repair takes a direct course and, if the individual survives, the destroyed tubular cells are replaced by new ones that are indistinguishable from those which originally lined the tubules. Since the function of such kidneys is entirely

normal, there is no reason to suppose that the new cells are inadequate in their particular function.

In other forms of Bright's disease, especially in the terminal stages of the hemorrhagic form, where all the structures and tissues of the kidney are af-

markedly atypical in their structure.¹ Since in the course of time, such atypical epithelium may replace the greater part of the tubular tissue and since the kidney ultimately fails, the question arises as to what part epithelial, that is tubular, dysfunction may

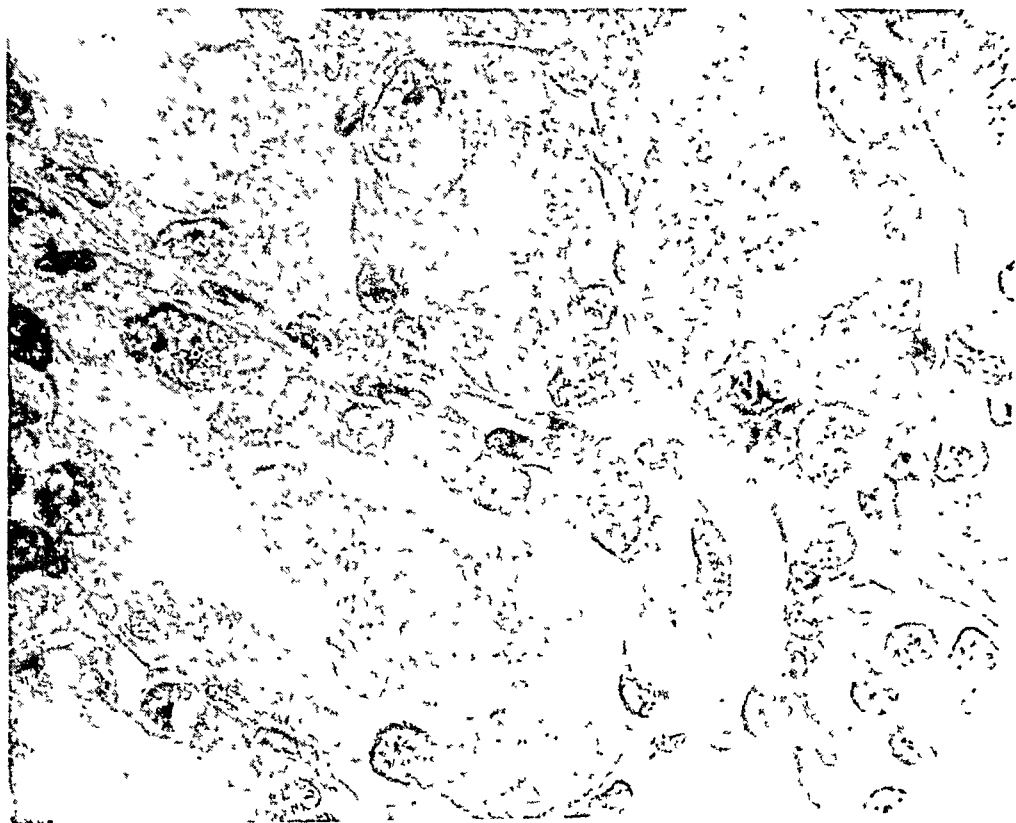


FIG. 2. Early immature regenerated epithelium of the convoluted tubules three days after sublimate poisoning.

ected, repair in the epithelial elements is complicated by the simultaneous occurrence of many other sorts of structural change. The more important of these are the growth of connective tissue and the development of arterial sclerosis. Under these conditions epithelial regeneration is abundant in its amount, but abnormal in nature, for the newly formed cells are

play in the production of the total organ's inadequacy. (Figure 1)

Here then is a problem for pathologic differentiation which demands more than the conventional answer that the pathologist often gives. The experiments which I shall describe illustrate an attempt at the more complete sort of answer.

Experimental nephritis was pro-



FIG. 3. Complete repair after sublimate poisoning. The convoluted tubules throughout the section are filled with dark staining mitochondria that are arranged in Heidenhain rods.

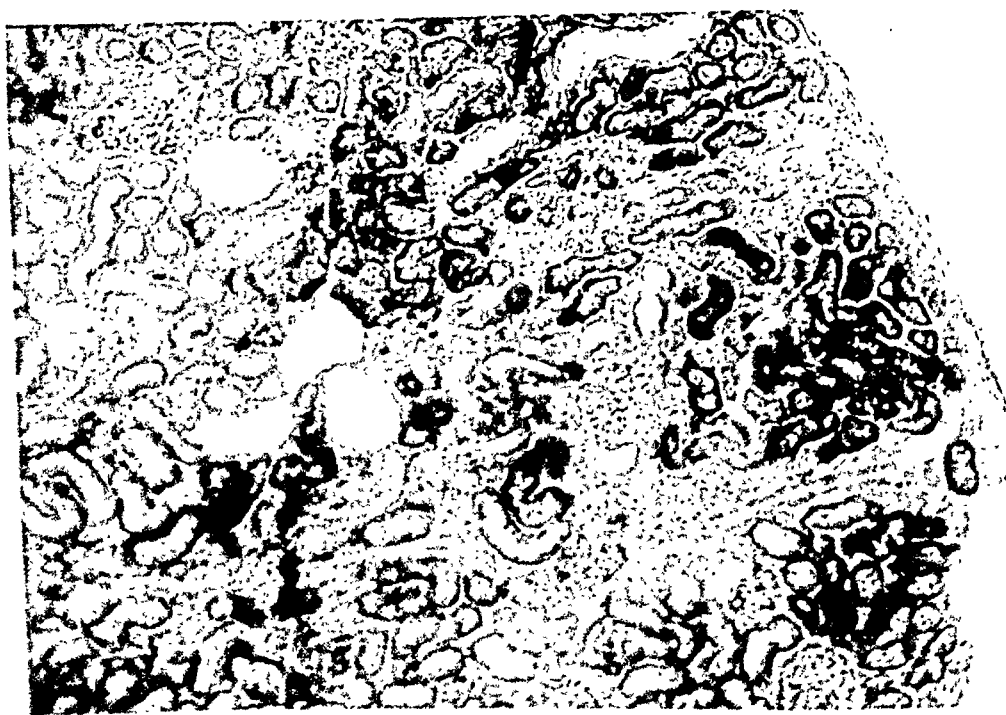


FIG. 4. Incomplete repair 146 days after uranium poisoning. Note irregularity in staining, caused by the patches of immature regenerated and atrophied epithelium which contains little or no electron staining. The dark tubules are lined by original cells that were not damaged by the toxic agent.

duced in guinea pigs by two toxic agents, corrosive sublimate and uranium nitrate.² That following sublimate poisoning is identical with the lesion found in man, and the regenerating epithelium, though at first irregular in size and shape (Figure 2), ultimately resembles exactly the original epithelium. After uranium administration, however, a development of connective tissue complicates the repair, so that a structural change in part at least analogous to the fibrosis of chronic Bright's disease in man is produced. The regenerated epithelium in such kidneys remains immature and morphologically atypical and so resembles that seen in the human kidney. Since the animal dies of renal

failure we have available for our examination under controllable experimental conditions the original problem I previously described.

Starting from the probably reasonable hypothesis that abnormal structure will result in abnormal activity, the pathologist assumes that these atypical regenerated cells cannot function properly and in his search for facts to bring forward in support of his assumption it occurs to him that, since there is considerable evidence that connects mitochondrial alterations with functional activity, it might be well to examine these cell structures.

This was done in our experimental lesions and it was found that in both forms of renal damage the early regen-



FIG. 5. Detail of immature regenerated cells from figure 4. The dark tubules are original undamaged ones filled with Heidenhain's rodlets. A is a normal collecting tubule in which mitochondria are normally scanty and the remaining irregularly lined tubules, B, are lined with the immature rodlet-free regenerated cells. (2)

—Courtesy of *Jr. Exper. Med.*

erated epithelium had only a small amount of mitochondrial substance and this not arranged in such definite cell organs as the rods of Heidenhain. In the mature regenerated cells of the completely repaired sublimate kidney, whose function was normal, all the characteristics of the normal mitochondria were ultimately devel-

tant part in cell activity, evidence has therefore been obtained that the atypical regenerated epithelial cell is functionally abnormal, and that this abnormality may play a part in the production of renal failure.

It is at this point that the pathologist often rests from his labors, either content with their fruits, or seeing no



—Courtesy of *Jr. Exper. Med.*

FIG. 6. Urea in normal convoluted tubules. All details are obscured by the dense black deposits. (2)

oped (Figure 3). But the atypical regenerated cells in uranium nephritis, where renal failure developed, remained immature in regard to their mitochondrial elements permanently, and never showed the presence of the Heidenhain rods, which characterize the normal original renal epithelial cell. (Figures 4 and 5) By the assumption that the mitochondria play an impor-

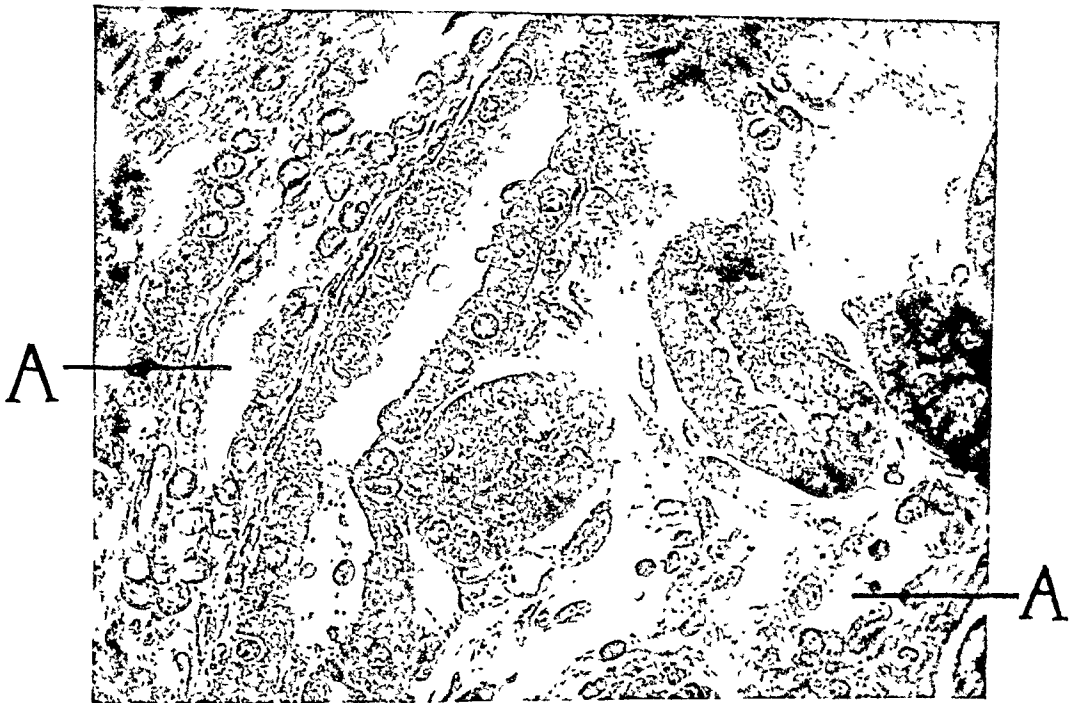
mediate way to proceed. An exact analysis of his contribution so far will show, however, that he has in fact added nothing to the evidence in the case, except detail and refinement of method; and the problem must still be stated as a hypothesis, namely that mitochondrial, i.e., structural, abnormality determines functional disturbance.

The final step in our search for an answer that completes the pathologic differentiation by correlating structure and function is, however, possible in the particular problem I am describing and this by means of direct objective evidence, where hypothesis plays no part.

Urea may be stained in situ in tis-

drial substance contained little or no urea. (Figures 6 and 7)

We need not be concerned with whether this means that the cells are failing to secrete or to absorb urea, but we can state definitely that, in a kidney which is failing to eliminate urea, the cells do not handle this sub-



—Courtesy of *Jr. Exper. Med.*

FIG. 7. Kidney after uranium poisoning stained for urea. Three original persisting convoluted tubules contain urea deposits. At A and B immature regenerated cells are seen almost free of this substance. For correlation of the structure and function of these cells compare figures 5 and 7. (2)

sues by its reaction with mercurous nitrate and, though like most micro-chemical reactions the procedure is not entirely specific, practical tests have shown that it is sufficiently so to demonstrate any considerable amount of urea in the kidney cells. Applied to the kidneys of uranium nephritis, it was found that the atypical regenerated cells that were poor in mitochon-

stance as do the original cells which possess a complex mitochondrial apparatus. And so this objective observation completes our pathologic differentiation by its demonstration of a correlation of structural and functional abnormality.

The first and specific conclusion of these findings, which is by analogy and must therefore be tentative, is that

tubular dysfunction plays a not unimportant part in the development of renal failure in terminal hemorrhagic Bright's disease, a statement which perhaps sounds more remarkable if the term "chronic glomerular nephritis" is used to designate the condition.

The second and general conclusion

suggests that the pathologist direct his efforts at differentiation towards a completion of his chains of evidence, for these must remain inadequate until his pathologic differentiation includes within its limits an objective correlation of both the structural and functional aspects of damage.

REFERENCES

- ¹ADDIS, T., and OLIVER, J.: The renal lesion in Bright's disease, 1931, Paul B. Hoeber, New York, 125-132.
²OLIVER, J.: A further study of the regen-

erated epithelium in chronic uranium nephritis; an anatomical investigation of its function. *Jr. Exper. Med.*, 1916, xxiii, 301-321.

Science and Practice in Bright's Disease*†

By T. ADDIS, M.D., F.A.C.P., *San Francisco, California*

THERE are in the main two sorts of men interested in Bright's disease. We may call them the clinical scientists and the clinical practitioners. They are separated by a difference in their aims. The ultimate aim of the clinical scientist is to disentangle from the chaos of the accidental and nonessential the general laws which govern the course of the disease. He searches for what is constant and measurable and turns aside from anything individual and concrete since such things are variable and cannot be measured. He reduces his observations on the living patient to something so cold, neutral, and generalized that it can be expressed in numbers, for his desire is to describe Bright's disease in abstract quantitative terms.

On the other hand, the purpose of the practitioner is to help the patient who has Bright's disease. He has to try to understand each patient and the special form which the disease takes in him, and so the individual and the variable, the very things which cannot be measured or expressed in numbers, are matters for his particular interest and attention, and since what he is

trying to do has no relation to absolute quantity it is sufficient for his purpose to recognize the presence and degree of abnormalities without defining them in precise numerical terms.

Now if we grant that there is this profound divergence in the respective purposes of the clinical scientist and the clinical practitioner the fact is worth considering that those who have the reputation of being the most up-to-date practitioners in Bright's disease are notoriously those who make a large use of the methods not of practice but of science. For are not their records full of all sorts of quantitative data, of figures which purport to represent precisely the quantities of various substances present in their patients' blood and urine? I think that an unbiased observer, analyzing this paradoxical situation, might come in the end to suspect that these figures were not present in the records because they were necessary for the work of the practitioner, but that they represented something really extraneous to his purpose which had been forced upon him. For such an observer would note that the practitioners who embellish their records with these quantitative facts do not value them so highly that they themselves are willing to take the trouble to make the measurements, for that sort of work is done by those who

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are neither clinical scientists nor practitioners. On reviewing the figures he would come on many instances of contradiction and palpable error and he would note that the revelation of such mistakes fails to disturb the calm of the practitioner. He would take into account how widespread is the popular worship of science in medicine and how general is the delusion that all medicine is scientific medicine, so that an ever-increasing number of patients believe that they cannot be comprehended or helped until they have been subjected to an elaborate and expensive system of physical and chemical measurement, and he would note also the persistent efforts of non-clinical scientists to reform the practitioner by making the introduction of the quantitative method into medicine relatively easy. So in summing up all such considerations he would have good grounds for the suspicion that these figures in the practitioner's records are really symbols of defeat, signs that the practitioner has been deviated from his purpose by a fashion in popular opinion. And, whatever may be thought of this, there is little doubt that such records are indications of the defeat of the clinical scientist, for here we find his methods, designed for abstract and general purposes, prostituted for the sake of what is transient and individual.

The majority of both clinical scientists and practitioners will probably revolt from this conclusion. They will attack the premise on which it rests by pointing out that there is no such person as the pure scientist or the pure practitioner and that each one of us has within him something of the science

tist and something of the practitioner. But can they argue that because we are thus compounded we should manifest something of the spirit of science while we are doing our practical work and be somewhat practical in our scientific endeavor? I do not think so. For the paths of practice and of science lead in opposite directions and they are straight and narrow ways on which only he makes progress whose mind is single and who for the time being is wholly scientific, with no thought for anything but quantity and generalization, or is wholly practical and attending only to what is qualitative and individual. My thesis is that the union of science and practice gives origin to an emasculated bastard lacking in the proper virtues of both its parents.

Having thus, in theory, divorced clinical science and practice, something may be said about the nature of the technical procedures peculiar to practice. For nothing of any but historical interest is to be said about the methods of clinical science. They are designed to answer some special question and when they have done that they are thrown away. All the methods we are now hearing about are already discarded and will never be used again, for in clinical science there is no standardization, no efficiency, no organization. Still less have such business virtues anything to do with practice in Bright's disease which, while it lives, is always new and individual and infinitely variable. But it can be said that the methods used in practice are in general of the "look and see" variety and that they usually present a vivid and concrete picture which has

color and body. Let us, for example, consider the sort of method which is useful to the practitioner in examining the blood of a patient with Bright's disease. He draws some blood from his patient's arm vein into a syringe which contains an anti-coagulant. After spinning it down in a centrifuge all he does is to look at it and in that glance, without thought or effort, he takes in the color and degree of turbidity of the plasma and the depth of the leukocytic layer and sees as in a colored graph that the red cells occupy half, or a third, or a fifth of the total volume. Then he takes some of the plasma, and on the addition of a reagent the depth of a color tells him whether there is little or much retention of urinary constituents. And all the while these vivid details are passing before him the living patient is still beside him, and his mind travels from the blood pictures to the patient and back again, subconsciously striving to create a larger and more inclusive picture, until at last, perhaps, it all falls together in a complete composition of the patient and the disease, and he may be able to see how he must act if he is to avoid doing harm or be able to do any good. That is the pure practice and art of medicine. Let no such practitioner feel any embarrassment because he is unable to tell some half-scientist half-practitioner consultant the exact number of red and white blood cells or the number of milligrams of creatinine and uric acid nitrogen in 100 c.c. of his patient's blood.

This warfare between the clinical scientist and the practitioner, both within and without us, goes on for-

ever, and neither side will finally prevail, for in this conflict only what is weak and superfluous on either side can be defeated while those things that remain stand firm. But it is a fruitful conflict only when the battle lines are clearly drawn. While we are practising medicine we must be only artists and while we are investigating disease we must be altogether scientists, for when we try to fight simultaneously under both flags we are double traitors. And so no practitioner need be deluded by the present uncomprehending worship of the scientific method into supposing that he can directly further his purpose by hiring someone else to provide him with numerical data on his patients. All he needs is to see with his own eyes his own clear pictures. One glance at a urine is worth more to him than a page of figures. Only let him make sure that the conditions under which he looks are not such as will blur and distort his picture. It is true that the microscopic examination of the urinary sediment can do for Bright's disease what the X-rays have done for diseases of the chest, but we can never see the renal lesion in the urinary sediment of our patients until we get them to abstain from fluids and give us timed collections of urine in order that the very elements of the picture may not dissolve and that we may see it undistorted by the accidental variations of time. The artist must understand the properties of the material with which he works but the composition is all his own and when it is completed it is seen at a glance, as a whole, and as a picture, not as an array of lifeless, disconnected, and abstract numbers.

Etiology and Pathogenesis of Hepatic Cirrhosis*†

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EXPERIMENTAL CIRRHOSIS OF THE LIVER

IMPROVED methods of microscopic technic permitting the study of finer changes in the structure of the liver, especially mitochondrial and reticulum stains, are responsible for recent additions to our knowledge regarding the pathogenesis of cirrhosis of this organ.

Fiessinger and Albot,¹ as well as Martin,² in studying in animals early stages of experimental lesions that eventually lead to cirrhosis of the liver, have shown that the first detectable changes invariably take place in the hepatic parenchyma and consist of mitochondriolysis and hyaline degeneration. This was found to be true regardless of the toxic agent used. Even colloidal silica, which according to Gye and Purdy³ initiates primary hypertrophy in the hepatic framework, was proven to cause lesions first in the parenchyma.⁴

The microscopic evidence of the uniform character of hepatic injury is supported by physiological observations on the metabolic activity of the

liver following the administration of various hepatic toxins. By following the blood sugar curves of rabbits after the administration of glucose, of glucose plus insulin, and of epinephrine, it has been shown in the author's laboratory that identical disturbances in hepatic metabolism were produced by phosphorus, chloroform,⁵ manganese, bacterial toxins, and even by India ink.⁶ Moreover, the changes in function were similar in kind, regardless of whether one large dose or many small doses of hepatic toxins were given.

The first effect of these substances is to produce an irritation of hepatic tissue resulting in hyperfunction which later changes into hypofunction. This finding is substantiated by Fiessinger's⁷ histological evidence that the hepatic cells in early poisoning are in a state of hyperfunction.

In human beings with various hepatic diseases the same disturbances of carbohydrate metabolism were demonstrated after insulin plus glucose and after epinephrine as those described in experimental animals.^{8,9,10}

The essential factor in the production of experimental cirrhosis is the repeated administration of hepatic toxins in sufficient doses to produce necrosis of some of the parenchymatous cells without causing death of the ani-

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mal. Agents causing fatty infiltration alone do not produce cirrhosis. The localization of lesions within the hepatic lobule depends upon the nature of the toxic agent employed. The extent of necrosis depends upon the dose of the toxin and upon the susceptibility of the individual animal at the time of administration.

Following necrosis of hepatic parenchyma two types of response to the injury can be observed. One is regeneration of hepatic cells from similar preëxisting cells. The other is sclerosis or a replacement proliferation on the part of the framework of the liver. The second process is ushered in by the appearance of islands of round-cell infiltration at the site of necrosis. Later these islands are succeeded by accumulations of fibroblasts in a thickened portion of the reticulum. From these foci, after repeated episodes of necrosis, strands of fibrous tissue extend into the parenchyma of the liver and may eventually join similar strands coming from other foci, giving a nodular appearance to the cut surface of the organ. At the same time the reticulum of the liver, in unaffected portions of the lobules also increases in density.

It is curious that even under the controlled conditions of an animal experiment with equal daily doses of a poison given by injection, the metabolic function of the liver undergoes periodic fluctuations for many months, testifying to the alternating predominance of necrosis and regeneration.⁶

HEPATOTOXINS

The list of substances which are known or suspected to cause cirrhosis

of the liver in man is a long one. The list of toxic agents which have been used to produce cirrhosis in animals is even longer, including over fifty different compounds. The necessary condition for the production of cirrhosis with any of them is long repeated exposure in doses sufficient to induce necrosis.

Among substances injurious to the liver, two classes deserve special mention. The first of these comprises alcoholic beverages to which unusual interest is attached because of their significance in the etiology of human cirrhosis and also because of their status in experimental cirrhosis. The connection between abuse of alcohol and cirrhosis of the liver is well established. Regarding the acute phase of the action of alcohol, Beckmann¹¹ showed that a single large indulgence results in a temporarily reduced capacity of the liver to metabolize lactic acid injected intravenously in the form of sodium lactate. Similar results were obtained by him¹² in animals subjected to poisoning by a variety of toxic agents including phosphorus and chloroform. Wallace,¹³ working with two tests of liver function, the quantitative van den Bergh test and the quantitative determination of urobilinogen in the urine, found definite evidence of hepatic injury following acute alcoholic intoxication. Von Bergmann¹⁴ and Eilbott¹⁵ were able to demonstrate under similar conditions that the power of the liver to excrete injected bilirubin is also impaired.

Turning to statistical evidence showing the effects of chronic alcoholism we see that in England and in Ger-

many, cirrhosis of the liver is more prevalent in urban than in rural populations, corresponding to the relative consumption of alcoholic beverages.¹⁶ For the same reason the disease is more common in men than in women, the only exception applying to prostitutes. The parallelism existing between deaths from cirrhosis and from alcoholism speaks for itself.¹⁷ The marked decline of cirrhosis in the United States during the first years of prohibition¹⁸ and in Germany during the war,¹⁹ due to difficulties in procuring alcohol, constitutes additional evidence linking alcohol with this disease. Finally the alcoholic history of a large majority of patients with cirrhosis cannot be disregarded. On the other hand the absence of this disease in most chronic drinkers can no more be used as evidence against the alcoholic etiology of cirrhosis than the absence of delirium tremens in a majority of alcoholics can be urged against the alcoholic origin of the latter affliction. The individual susceptibility of organs plays a large part in both conditions.

In the laboratory the majority of observers were unable to produce cirrhosis of the liver by alcohol alone. On the other hand when alcohol is given in combination with other toxic substances, (carbon tetrachloride,²⁰ bacterial toxins,²¹ phosphorus²²), the damage to the liver is augmented. The dose of either that alcohol in itself is a weak hepatic toxin producing cirrhosis only in conjunction with another agent in the body and brought about by the action of that agent is to be ascertained by experiments specific to

the action of other toxic agents. In either case the result is the same.

The second group of substances, to which in contrast to alcohol little attention has been paid in connection with cirrhosis of the liver, is the group of inert colloids. Such substances as India ink, colloidal silica, Trypan blue, etc. are being used in biological experiments to impair the function of the reticulo-endothelial system. The changes produced by injections of these substances, such as diminution in the titre of antibodies, etc., are ascribed to a so-called "block" of this system on the assumption that chemically inert bodies in colloidal suspension are powerless to injure parenchymatous organs. However, in some recent experiments,⁶ the author found with surprise that after three injections of India ink the tolerance for sugar and the response of rabbits to epinephrine were affected as markedly as after any of the "specific" hepatic poisons. In agreement with this finding is the description by Albot¹ of hyaline degeneration in the liver of animals following as few as two injections of India ink.

A plausible explanation of the mechanism of such an injury is that particles of India ink, by filling the Küpfer cells and other units of the reticulo-endothelial system, are exposing the hepatic parenchyma to the influence of poisons circulating in the blood. If such is the true mechanism it would be comparable to the action of alcohol in rendering the liver more susceptible to the effect of toxins. It is also of interest that in individuals with pulmonary tuberculosis and dilated cir-

hosis of the liver has been described due to the probable action of particles of coal and quartz on this organ.^{22,23,24,25} That pigmentary cirrhosis of the liver probably also belongs to this group is suggested by the experimental production of cirrhosis by injections of hemoglobin and a number of hemolytic substances.

THE UNITARY CONCEPTION OF HEPATIC CIRRHOSIS IN MAN

Knowing that cirrhosis of the liver is the result of an interplay of necrosis, regeneration, and sclerosis, it is not difficult to see that the relative prominence of these processes accounts for the terminal picture seen by the clinician and by the pathologist. Experimentally this can be demonstrated by the example of chloroform which, depending on the mode of administration, will produce either a picture

closely simulating acute yellow atrophy or cirrhosis.

In the clinic we have at one extreme the toxic cirrhosis of Mallory caused by repeated attacks of subacute yellow atrophy of the liver, the end-result, that is, of massive necrosis and extremely vigorous regeneration of hepatic parenchyma with little interstitial fibrosis. (Figure 1) At the other end of the scale we see the atrophic type of portal cirrhosis, resulting from several decades of steady drinking in susceptible persons and characterized by extensive penetration of fibrous tissue into the hepatic lobules. (Figure 2) The occurrence of all possible grades of transition between these outstanding types of cirrhoses* is of fundamental significance. If further proof is desired, a perusal of the more elaborate systems

*"Luetic cirrhosis" or, more correctly, lues of the liver is not considered here.

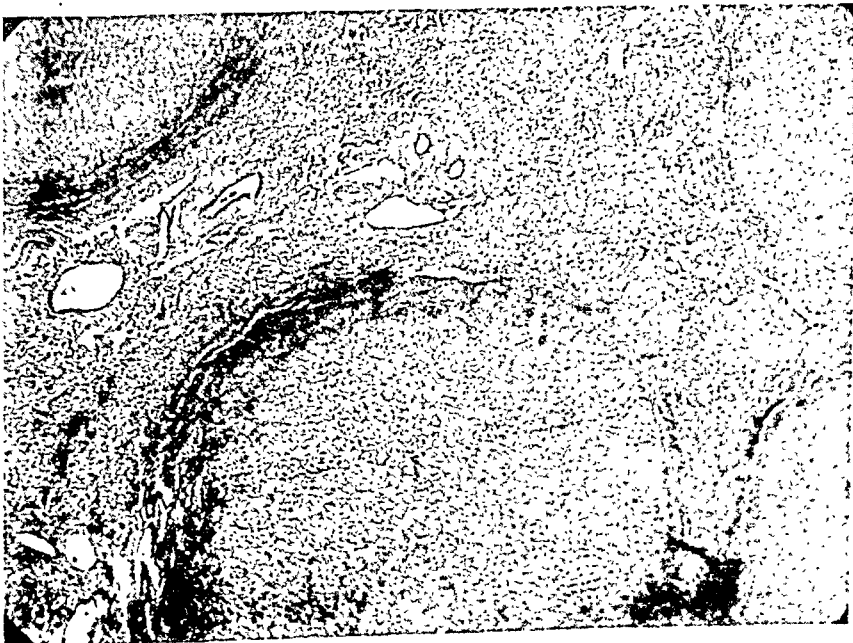


FIG. 1. Toxic cirrhosis of the liver showing great loss of hepatic substance and adenomatoid nodules of regenerated cells.

of classification will show how blurred the distinctions really are between the various types of cirrhosis. Especially misleading are the classifications taking into account the size of the liver since an enlargement of this organ can be brought about by active regeneration, fatty infiltration, or hyperemia, regardless of the other features of any given case. Also, as shown by Bollman and Mann,²⁶ in experimental cirrhosis of the dog some lobes of the liver may be atrophied while adjacent lobes in the same animal are hypertrophied.

The unitary conception of the genesis of cirrhosis of the liver is important because it focuses attention on the necrotizing agent instead of on the anatomical diagnosis and, in the individual case, is conducive to earlier

recognition and treatment of this disease.

PROSPECTS OF THERAPY IN CIRRHOSIS OF THE LIVER

In conclusion a few words may be said regarding therapeutic possibilities in cirrhosis of the liver. In animal experiments even extensive cirrhosis with ascites and jaundice recedes soon after the administration of the poison is stopped. The same improvement has been reported in individuals who developed cirrhosis with ascites from prolonged medication with arsenicals.²⁷ Such observations, taken together with other suggestive facts from the clinic and the autopsy table, make it probable that many patients with this disease, especially in the alcoholic groups, recover when the advice of a physician

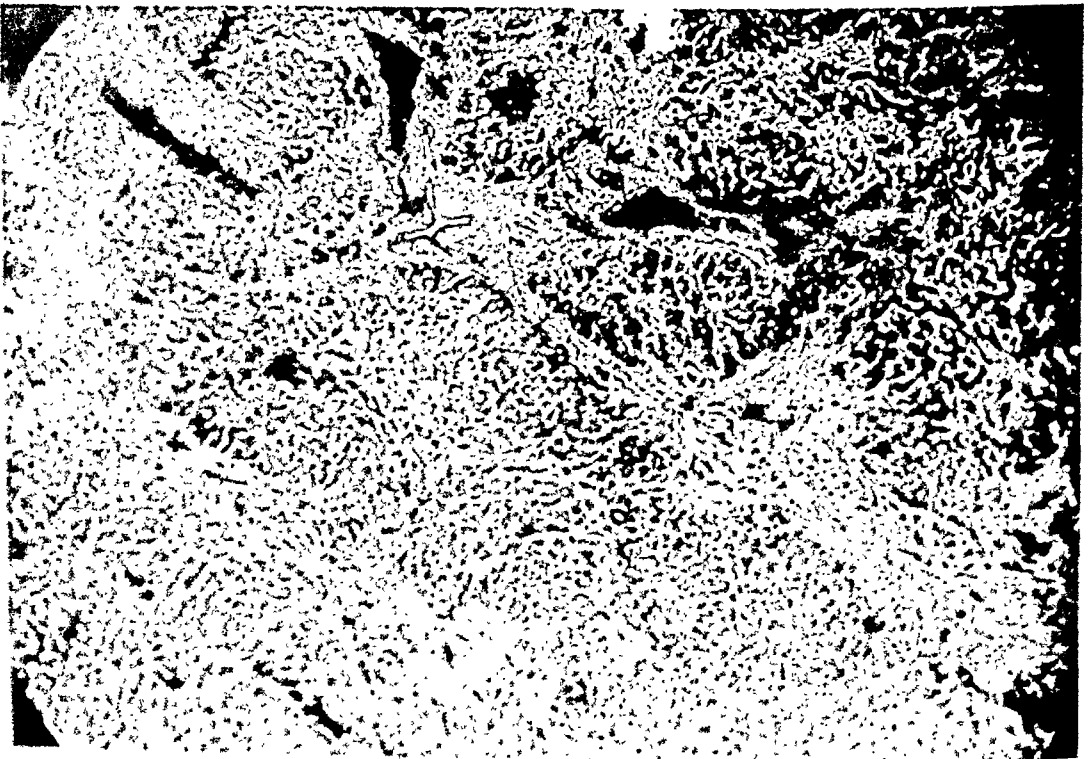


Fig. 2. A cross-section of the liver characterized by extensive diffuse fibrosis.

or an attack of jaundice has influenced them to stop the abuse of alcohol.

The intractability of the easily recognizable stages of cirrhosis depends upon the fact that the "classical" symptoms of this disease are really signs of grave decompensation which supervenes only after regeneration has been for some time falling behind necrosis. The main factors responsible for the slowing down of regenerative processes in the liver are diminution in blood supply and extensive fibrosis. The tendency which becomes manifest in middle age, to replace parenchyma by connective tissue, probably favors the usual appearance of cirrhosis during this time of life.²⁸

SUMMARY

The earliest lesions leading to experimental cirrhosis of the liver are

always found in the hepatic parenchyma. Any toxic agent causing necrosis of the parenchymatous cells of the liver will on repeated administration produce cirrhosis of this organ. Alcohol and inert colloids are discussed as etiological factors in cirrhosis.

Following necrosis of hepatic tissue, regeneration of parenchyma and proliferation of the framework of the liver take place. The relative prominence of these two processes, as well as the dose of the toxin and its chemical nature, determine the clinical and pathological end-picture of cirrhosis.

The unitary conception of the genesis of the various types of cirrhosis of the liver furthers earlier recognition and treatment of this disease by focusing attention on the toxin involved.

BIBLIOGRAPHY

- ¹FIESSINGER, N., and ALBOT, G.: Sur le développement et le groupement des cirrhoses du foie, *Ann. d'anat. path.*, 1929, vi, 895-930.
- ²MARTIN, J. F.: Recherches expérimentales sur l'histogénèse des stades initiaux de la cirrhose hépatique, *Ann. de méd.*, 1927, xxi, 89-143.
- ³GYE, W. E., and PURDY, W. J.: The poisonous properties of colloidal silica, *Brit. Jr. Exper. Path.*, Lond., 1924-25, v, 238.
- ⁴ALBOT, G.: Les hépatites diffuses expérimentales (atrophie aiguë et cirrhose expérimentales), *Ann. d'anat. path.*, 1931, viii, 437-475.
- ⁵ALTHAUSEN, T. L., and THOENES, E.: The influence on carbohydrate metabolism of experimentally induced hepatic changes, I, II, and III, *Arch. Int. Med.*, 1932, l, 46-57, 58-75, 257-268.
- ⁶ALTHAUSEN, T. L.: On metabolic changes accompanying hepatic lesions which lead to cirrhosis of the liver. (To be published shortly).
- ⁷FIESSINGER, N.: Contribution à l'étude des dégénérescences de la cellule hépatique au cours de certaines intoxications brutales chez les batraciens, *Compt. Rend. Soc. de biol.*, Paris, 1909, lxvi, 391, 426, 494.
- ⁸ALTHAUSEN, T. L., GUNTHER, L., LAGAN, J. B., and KERR, W. J.: Modification of the dextrose tolerance test as an index of metabolic activity of the liver, *Arch. Int. Med.*, 1930, xlvi, 482-493.
- ⁹ALTHAUSEN, T. L., and MANCKE, R.: Kombinierte Leberfunktionsprüfung (Insulin-, Glykose-, und Wasserbelastung), *Deutsch. Arch. f. Klin. Med.*, 1931, clxx, 299.
- ¹⁰BRULÉ, M., and ALTHAUSEN, T. L.: Exploration fonctionnelle du foie par divers procédés d'épreuve de la fonction glyco-régulatrice, *Presse méd.*, 1932, xl, 164-166.

- ¹¹BECKMANN, K.: Klinische Enfiahrungen mit der Leberfunktionsprüfung durch Milchsäurebelastung, *Ztschr. f. klin. Med.*, 1929, cx, 163-175.
- ¹²BECKMANN, K., and MIRSALIS, J.: Der Milchsäuregehalt des Blutes nach Milchsäureinjektion bei experimentellen Leberschädigungen, *Deutsch. Arch. f. klin. Med.*, 1928, clix, 129-146.
- ¹³WALLACE, R. P.: Liver injury in acute alcoholic poisoning, *Proc. Soc. Exper. Biol. and Med.*, 1927, xxiv, 598-599.
- ¹⁴VON BERGMANN, G.: Zur funktionellen Pathologie der Leber insbesondere der Alkohol-Aetiologie der Cirrhose, *Klin. Wchnschr.*, 1927, vi, 776-780.
- ¹⁵EILFOTT, W.: Funktionsprüfung der Leber mittels Bilirubinbelastung, *Ztschr. f. klin. Med.*, 1927, cvi, 529-560.
- ¹⁶UMBER, F.: Die Leberzirrhose, in BERGMANN, G., and STAEHELIN, R.: *Handbuch d. inn. Med.*, 1926, iii, Heft 2, J. Springer, Berlin. 90-110.
- ¹⁷STEVENSON, T. H. C.: The mortality of alcoholism, *Practitioner*, Lond., 1924, cxiii, 270-280.
- ¹⁸MILLER, J. L.: The effect of prohibition on the incidence of portal cirrhosis, *Jr. Am. Med. Assoc.*, 1921, lxxvi, 1646-1647.
- ¹⁹LAMSON, P. D., GAEDNER, G. H., GUSTAFSON, R. K., MAIRE, E. D., MCLEAN, A. J., and WELLS, H. S.: The pharmacology and toxicology of carbon tetrachloride, *J. Pharm. and Exper. Therap.*, 1923, xxii, 215-288.
- ²⁰RAMOND, F.: Pathogénie des cirrhoses du foie; recherches expérimentales, *Presse méd.*, Par., 1897, v, 178-180.
- ²¹FISCHLER, F.: Über die praktische Auswertung einiger neuerer Erkenntnisse über die Funktionen der Leber, *München. med. Wchnschr.*, 1925, lxxii, 1910.
- ²²WELCH, W. H.: Cirrhosis hepatis anthracotica, *Johns Hopkins Hosp. Bull.*, 1891, ii, 32.
- ²³ROLLESTON, SIR H., and MCNEE, J. W.: *Diseases of the liver, gall-bladder and bile-ducts*, 3 Ed., 1929, MacMillan and Co., London, 330.
- ²⁴ALBURGER, H. R.: Anthracosis of the liver in pulmonary tuberculosis, *Proc. Path. Soc. Phila.*, 1905, n.s., viii, 137-140.
- ²⁵ADAMI, J. G.: Cirrhosis of the liver, *Sajous' analytic cyclopedia of practical medicine*, 1920, 8 rev. ed., F. A. Davis Co., Philadelphia, iii, 396-460.
- ²⁶BOLLMAN, J. L., and MANN, F. C.: Experimentally produced lesions of the liver, *Ann. Int. Med.*, 1931, v, 699.
- ²⁷O'LEARY, P. A., SNELL, A. M., and BANNICK, E. G.: Portal cirrhosis associated with chronic inorganic arsenical poisoning; report of 2 cases, *Jr. Am. Med. Assoc.*, 1928, xc, 1856-1859.
- ²⁸CHVOSTEK, F.: Zur Pathogenese der Leberzirrhose, *Wien. klin. Wchnschr.*, 1922, xxxv, 381; 408.

Aleukemic Myelosis with Osteosclerosis*†

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IN 1904 Albers-Schönberg¹ first described the roentgenologic picture of a disease of the skeletal system characterized by transformation of the medullary canal and spongy portions into compact bone. The condition has since been described under various names: Albers-Schönberg disease, osteosclerosis, osteopetrosis, marble bones, Marmorknocken, Marmorskelle, etc. According to Karshner,² who has recently reviewed the subject, osteosclerosis is hereditary and is due to a primary dyscrasia of the mesenchyme, resulting in abnormal and excessive bone formation. The essential lesion is an increase in thickness of the hard, cortical bone, with condensation and broadening of trabeculae and crowding of the marrow elements, which are often replaced by fibrous tissue. There is no apparent relation to syphilis or vitamin deficiency. Commonly found in infancy and childhood, the primary changes are known to persist without symptoms well into adult life. Of cases reported in the literature, about one-third have shown

blood dyscrasias which may be classified as aleukemic myeloses; the remainder have been accompanied either by an anemia or by no change in the circulating blood.

From the literature, we have been able to collect twenty-four cases of generalized osteosclerosis with aleukemic myelosis. Of these, nineteen are described in sufficient detail to be included in the summary of table 1. In addition, incomplete reports of cases which fall into this group are given by Baumgarten²¹ and Schmorl.²² Of the twenty-one cases, that of Goodall appeared in the English literature, the remainder in the German. The postmortem observations of still another case are described in the Italian literature by Pastore.²³

From table 1 it is seen that the association of osteosclerosis with a leukemoid blood picture has been observed with about equal frequency in the two sexes and is not limited to any particular age group: the age of patients has varied from ten weeks to seventy-six years, with each decade represented by one or more cases. In adults at least, the condition has been chronic. Most of the patients give a long history of splenomegaly, and cases followed for a number of years show but little change in the clinical

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TABLE I

AUTHOR	SEX	AGE	ANEMIA	WBC	MYELOCYTES	NORMOBLASTS	ENLARGEMENT OF SPLEEN	ENLARGEMENT OF LIVER	ENLARGEMENT OF LYMPH NODES	OSTEOSCLEROSIS
Heuck ²	M	24	Severe	80,000	+	+	+	+	+	+
v. Jaksch ⁴	F	24	Severe	10,000	+	+	+	+	+	+
				70,000						
Askanazy ⁵	M	53	Severe	14,000	+	+	+	+	—	+
Nauwerck & Moritz ⁶	F	37	Severe	11,000	+	+	+	+	—	+
Assmann ⁷	M	53	Moderate	14,000	+	+	+	+	+	+
Lehndorff & Zak ⁸	M	76	None	47,000	+	—	+	+	+	+
Albers-Schönberg ¹	M	26	Moderate	6,000	+	+	+	+	+	+
Goodall ⁹	F	10	Severe	75,000	+	+	+	+	—	+
		wks								
Diel & Levy ¹⁰	F	62	Severe	5,200	+	+	+	+	+	+
Laurell & Wallgren ¹¹	M	12	Mild	8,000	+	—	+	—	—	+
Oesterlin ¹²	?	2	Severe	11,000	+	+	+	+	—	+
Nadolny ¹³	M	4	Moderate	62,000	+	+	+	+	+	+
Kraus & Walter ¹⁴	F	3	Severe	12,000	+	+	+	—	—	+
Bernhardt ¹⁵	M	26	Severe	Normal	+	+	+	—	+	+
Hagedorn ¹⁶	M	60	Severe	6,000	+	+	+	+	+	+
Reiche ¹⁷	F	32	Moderate	20,000	+	+	+	+	—	+
Jores ¹⁸	F	34	Mild, later severe	12,000	+	+	+	+	—	+
				20,000						
Mayros ¹⁹	F	38	Mild	6,000	+	+	+	—	+	+
Schwarz ²⁰	F	42	Severe	20,000	+	—	+	—	—	+
				40,000						

picture other than a slowly progressive anemia. Jores' patient was observed over a period of twelve years; the patient described by Albers-Schönberg in 1904 was reported by Reiche¹⁷ in 1915 and again by Lorey and Reye²⁵ in 1923.

The requirements for the diagnosis of aleukemic myelosis in these patients are fulfilled by extramedullary proliferation of the myelogenous apparatus in the spleen and other organs, with young cells in the peripheral blood in the presence of a normal or but slightly elevated total white blood cell count. It may be seen that six of the patients described in the literature exhibited total counts of over 20,000 per cu. mm. It should be noted, however, that three of these patients were very young, and in others the leuk counts were

apparently terminal. Splenomegaly is probably the most striking clinical manifestation of the syndrome, and in our cases, as in others, it was the presence of splenic tumor that led the patients to seek medical advice. In autopsied cases the spleen has been found to weigh from 1400 to 2700 grams; histologically the enlargement is seen to be due to infiltration and proliferation of myelogenous cells. The less marked enlargement of liver and lymph nodes is due to a similar myelometaplasia. In contrast to chronic myelogenous leukemia the percentage of myelocytes and myeloblasts in the peripheral blood is not high, in most cases not over 20 per cent. A case recently reported by Zyphrin²¹ is unusual in that the leukemic disturbance was of the lymphoid type. The

patient was a man of 42 years, who exhibited generalized enlargement of lymph nodes, splenomegaly and hepatomegaly, moderate anemia and white blood cell counts from 4,700 to 87,000 with 65 to 70 per cent lymphocytes. At autopsy the lymph nodes throughout the body were found to be enlarged and there were lymphoid infiltrations of the spleen, liver, and bone marrow; the bones showed a generalized osteosclerosis similar to that observed in other cases.

The anemia, which varies greatly in severity from case to case, is always of a highly regenerative type. The increased activity of the remaining marrow and the severity of the strain on the impoverished erythropoietic system is reflected in the peripheral blood by the presence of normoblasts, punctate basophilia, polychromatophilia, and changes in the size and shape of the red blood cells. We have no evidence of ectopic, extramedullary red blood cell formation in these cases, but, as Doan²⁷ has pointed out, it is entirely possible that this may occur when unusual demands are made on the blood forming system.

The case reports which follow are apparently the first of this type to appear in the American literature.

CASE I

W. McC., a white carpenter 51 years old, was admitted to Barnes Hospital May 12, 1930, complaining of a mass in the left side of the abdomen. His attention had first been called to this mass seven years before by a dull aching pain in the upper abdomen. Two years later he was admitted to his local hospital because of gradual loss of weight and strength; he was told that he had a disturbance of the white blood cells, and on exploratory laparotomy a huge

spleen was found. At that time he received six exposures to X-ray and eight arsenical injections; he gained weight and strength, was able to return to work, and remained in fair health for almost five years. During the four months before admission to the hospital, however, he had again been losing weight and strength and had had constant pain in the left side of the abdomen. In the past his health had always been good and the family history revealed nothing of significance.

On examination the patient appeared chronically ill; the complexion was sallow, the skin and mucous membranes pale. The inguinal lymph nodes were slightly enlarged but there was no general lymphadenopathy. Examination of the head showed nothing abnormal. The lungs were clear, the heart normal. Blood pressure was 100 mm. Hg systolic, 60 diastolic. The peripheral arteries were markedly thickened. A greatly enlarged, hard spleen was found, extending past the midline and downwards to the iliac crest. The liver was slightly enlarged to percussion. The prostate was normal. The extremities showed nothing unusual.

Blood hemoglobin was 65 per cent (Sahli), red blood cells numbered 3,240,000 per cubic millimeter, white blood cells 10,300. The smear showed variation in size and shape of erythrocytes, many normoblasts and stippled cells. Differential white blood cell count revealed the presence of myelocytes and young granular cells. The blood findings are shown in detail in table 2. The urine on several occasions showed nothing unusual; in particular it contained no Bence-Jones protein. Stool examinations were negative. The blood Kahn was negative. Roentgen examinations of the skeletal system showed extensive changes, with general increase in density and multiple small areas of *relative* rarefaction. Figure 1 shows these changes in the bones of the pelvis. The areas of relative rarefaction were considered by the roentgenologist to be representative of bone of normal density, with darker areas representing bone of increased density. Striking changes of similar character were observed in the clavicles and ribs and in the vertebrae. The films also showed marked calcification of arteries. Blood calcium was 10.5 mg. per cent, uric acid 8 mg. per cent.

TABLE II
Blood findings in Case 1.

DATE	HR %	RBC IN MILLIONS	WBC	EOSINOPHILES	MYELOCYTES	JUVENILES	STABS	SEGMENTS	LYMPHOCYTES	MONOCYTES	RBC
5-12-30	65	3.24	10,300	1	5	5	5	25	59	2	Anisocytosis and poikilocytosis. Many nucleated red blood cells and stippled red blood cells.
5-16-30	60	3.84	9,500	2	9	0	6	22	57	4	
5-17-30				1	18	15	9	24	32	1	
12- 4-30	60	3.94	5,200		12	14	2	10	56	6	
1- 2-31	65	3.25	9,200		12	6	8	48	20	2	

non-protein-nitrogen 40 mg. per cent. Gastric analysis showed a normal acid curve. Phenolsulphonephthalein excretion was 50 per cent in two hours. The basal metabolic rate was plus 19 per cent. Material obtained on splenic puncture showed many myelocytes.

The patient's course in the hospital was afebrile and uneventful except for diagnostic procedures. He received one exposure to deep X-ray therapy without apparent benefit.

Six months later he reentered the hospital because of dull pains in the back and legs. Findings on examination were similar in all respects to those on the previous admission. After a biopsy of a rib the patient was again discharged; he has since moved from the vicinity of St. Louis and the authors have not been able to trace him.

Pathological report by Dr. Howard McCordock revealed the following: "The gross specimen consisted of a piece of rib about



Fig. 1. The rib specimen from Case 1, showing nothing remarkable due to the gross appearance of the rib. The rib is of the type of a costal cartilage.

one inch in length. On cross section there was no definite marrow cavity. The medullary cavity appeared to have been replaced by newly formed bone tissue. In this, however, there were small red flecks representing the remains of marrow spaces. The increased hardness of the rib was evident when it was cut, for it offered as much resistance to the

bone which stained red with the eosin. Alongside of this new bone formation there could be seen evidences of bone destruction with large numbers of multinucleated osteoclasts resting in excavations situated along the edge of the bone trabeculae. The bone marrow spaces almost everywhere were filled with a loose cellular connective tissue. In

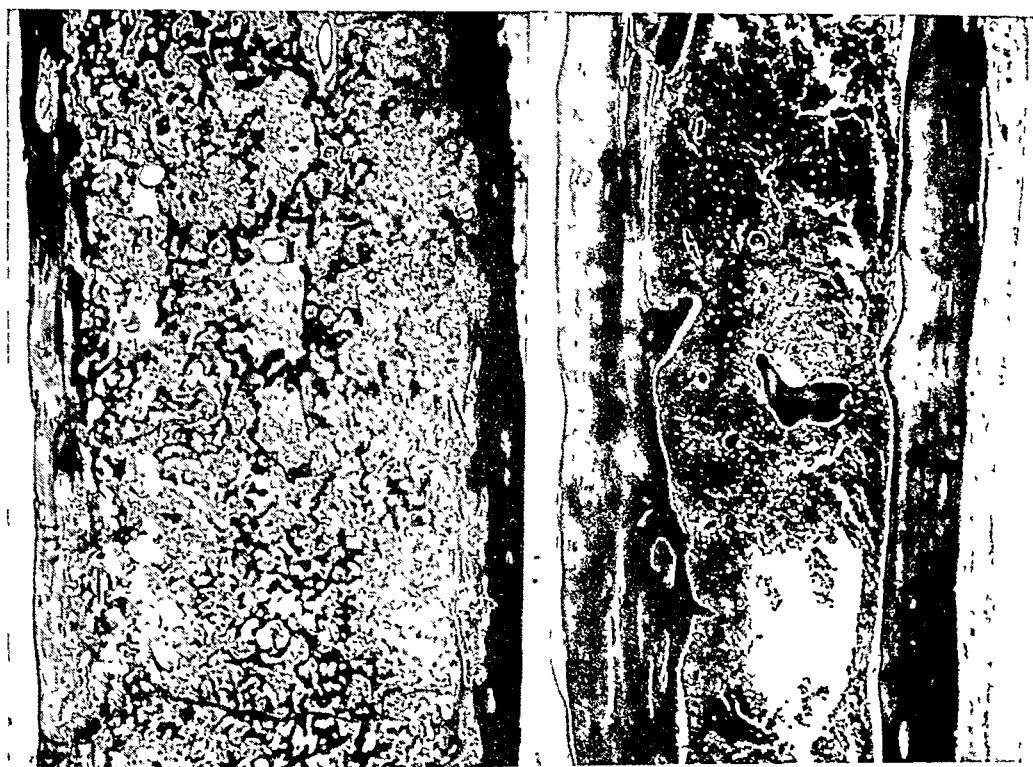


FIG. 2. *Left*: Photomicrograph of rib of Case 1, showing osteosclerotic invasion of the medullary cavity. *Right*: Normal rib, showing relatively wide cortex and normal medullary cavity without obvious trabeculation.

saw as the outer table of the skull usually does. The cut surface was of ivory-like density.

"After decalcification sections were made and stained with hematoxylin and eosin and Giemsa stain. The thin bone trabeculae that normally traverse the marrow cavity were greatly increased in number and thickened. This produced a dense bony structure in which there were only tiny remnants of the marrow spaces. All this newly formed bone was well calcified. One could often make out the original bone trabeculae by their deeper blue stain, and surrounding these there was a thick layer of newly formed

places in the meshes of this connective tissue there might be seen small nests of blood forming cells among which one could recognize myelocytes, polynuclear leukocytes, normoblasts, red blood cells, and a few megakaryocytes. On the whole, however, the fibrous marrow predominated and the islands of hematopoietic tissue were few and far between. *Diagnosis*: Osteosclerosis with fibrosis of bone marrow."

CASE II

J. J., a farmer 48 years old, was admitted to Barnes Hospital August 7, 1930, complaining of a mass in the left side of the

TABLE III
Blood findings in Case 2.

DATE	Hb %	RBC IN MILLIONS	WBC	BASOPHILES	^a / ₂ EOSINOPHILES	MYELOCYTES	JUVENILES	STABS	SEGMENTS	LYMPHOCYTES	MONOCYTES	RBC
8- 7-30	60	3.3	14,000	0.5	1.5	45	14	19	10	10	0	Anisocytosis and poikilocytosis. Many nucleated red blood cells and stippled red blood cells.
8- 8-30					2	41	11	13	13	16	4	
8-11-30			14,800			20	24	21	17	14	4	
8-14-30	60	3.36	15,400			17	29	24	14	16	0	
8-20-30			14,400			30	17	25	13	11	2	
11-29-30	55	3.35	11,400			42	8	8	20	22	0	
12- 4-30				0	2	44	10	8	14	16	6	
12- 8-30			14,500	4	8	16	6	8	33	21	4	

the ribs and clavicles similar to those observed in the pelvic bones. Material from splenic puncture showed many myelocytes.

A small therapeutic dose of X-ray was followed by a drop in the white blood cell count from 14,000 to 10,000 per cubic millimeter; this was considered a contraindication to further radiotherapy. The patient returned three months later with but little change except for the presence of ascites; there was no dependent edema. Paracentesis abdominalis was performed and five liters of yellowish green fluid obtained. The fluid contained 1200 cells per cubic millimeter and had a specific gravity of 1.020. Differential count of the cells in the ascitic fluid showed 20 per cent myelocytes, 15 per cent segmented polymorphonuclear leukocytes, 6 per cent lymphocytes and 59 per cent unclassified cells.

After discharge from the hospital it was necessary to perform a paracentesis about every ten days. In a recent letter from the patient's physician it was learned that a blood examination in July, 1931, showed practically the same picture as that observed by the authors and that the patient died in August, 1931, of a gastric hemorrhage.

DISCUSSION

These two patients exhibit a striking similarity in history and in physical and laboratory findings. Both presented the complaint of a mass of long duration in the left side of the abdomen. Although the history was of but

two years' duration in Case 2, it is not unlikely that the splenomegaly was of much longer standing. In view of the fact that the spleen was quite large when first noted and increased but little in size during the following two years, it is reasonable to suppose that the spleen had been enlarged for some time, but that in the absence of other symptoms this enlargement had not been discovered. The splenomegaly overshadowed all other physical findings, and splenic puncture indicated that the marked enlargement was due to myelogenous infiltration. The presence of myelocytes in the ascitic fluid in the second patient suggested the presence of myeloid metaplasia in the peritoneum and probably in the liver. In both cases the roentgenologic findings were considered most suggestive of metastatic carcinomatosis of bone with reactive sclerosis, but detailed investigation in each case failed to demonstrate any evidence of a primary carcinoma. In the first patient rib biopsy revealed the true nature of the bone disturbance and definitely established the diagnosis. The second patient refused to submit to biopsy of bone, and, although unlikely, the pos-

sibility of metastatic miliary carcinomatosis of bone cannot be definitely excluded. It is of interest that both patients showed clinical evidence of rather marked peripheral arteriosclerosis.

In consideration of the pathogenesis

with the cortex of the long bones partially replaced by cancellous tissue of dirty brick red color, so that the bone on section showed only a narrow cortical border. Similar cases have been described by others. A reactive sclerosis of bone secondary to true



FIG. 4. Roentgenogram of pelvic bones in Case 2, showing marked trabeculation and changes almost identical to those of figure 1.

of this syndrome, there is a difference of opinion as to whether this is primarily a disease of blood and blood forming organs or of bone. Bone changes have been described in true leukemia, but here the marrow cavity is usually increased in extent at the expense of the cortical bone in direct contrast to the obliteration of marrow in osteosclerosis. For example, in 1900 Mott^{2*} described a case of leukemia with ear changes in which the petrous bone showed rarefaction; the bones throughout the body showed changes,

leukemia has been said to occur, but we have been unable to find case reports in which this relationship has been established.

The studies of Karshner² indicate that the type of bone disturbance seen in osteosclerosis is hereditary; apparently the character and degree of change in the erythropoietic and leukopoietic systems depend on the extent and severity of marrow involvement. The myelogenous deposits in spleen, liver, and lymph nodes may well be regarded as a compensatory mechan-

ism. Donhauser²⁹ has considered that the spleen may act as a hematopoietic organ as exemplified in the autopsy observations of a 58-year-old man who showed splenomegaly considered secondary to a primary sclerosis of bone marrow. The marrow was replaced by lymphoid cells and fibroblasts but the bone changes of osteosclerosis were not present. The spleen contained cells normally found in the bone marrow, and the author concluded that the spleen had reacted to the destruction of marrow by resuming its hematopoietic function.

Osteosclerosis may be compared to metastatic carcinomatosis of bone as a primary factor in the pathogenesis of leukemoid disturbances. Weber³⁰ described under the title, "A Case of Osteosclerotic Anemia or Leukemia", a man of fifty-eight in whose bones the cancellous tissue was solid and rocklike with the medullary canals partially filled with hard bone and fibrous tissue. This was first regarded as true osteosclerosis but further microscopic study of autopsy material showed that the osteosclerosis was in reality a reactive change to metastatic generalized miliary carcinomatosis of bone, secondary to a small primary carcinoma of the prostate.³¹ In many cases described in the literature as unqualified aleukemic myelosis, aleukemic leukemia, or pseudoleukemia, there is no mention made of clinical or pathological examination of the skeletal system. It is possible that aleukemic myelosis is not a clinical entity but is a secondary and sympto-

matic result of another disease localized in the bone marrow.

In the differential diagnosis of these cases leukemia is usually considered. However, the long duration of symptoms and of splenomegaly, the low total count, and the relatively small percentage of young cells in the differential formula should make one wary of diagnosing a true leukemia. Roentgenologic study of the skeletal system is indicated in all patients with this type of blood dyscrasia. As we have seen, the roentgenologic picture of osteosclerosis may simulate that of metastatic carcinomatosis. Here again the long duration and chronicity of the disease, together with the lack of evidence of primary tumor or of metastasis to other regions, indicate that the bone change is not a metastatic one. The diagnosis may be definitely established by biopsy of bone, or, as has been done in some instances, by sternal puncture.

There is no known type of therapy which influences the course of osteosclerosis. If, as we believe, the leukemoid changes are in the nature of a compensatory mechanism, it is best not to attempt to influence the leukopoietic apparatus by means of deep X-ray therapy or by other measures commonly used in the treatment of leukemia. Treatment, in the light of our present conception of the etiology of the disease, should be symptomatic and directed at the improvement of the general health of the patient.

REFERENCES

- ¹ALBERS-SCHÖNBERG, H. E.: Röntgenbilder einer seltenen Knochenerkrankung, München. med. Wchnschr., 1904, li, 365.
²KARSHNER, R. G.: Osteopetrosis, Am. Jr. Roentgenol., 1926, xvi, 405-419.

- ³HEUCK, G.: Zwei Fälle von Leukämie mit eigenthümlichem Blut-resp. Knochenmarksbefund, Virchow's Arch. f. path. Anat., 1879, lxxviii, 475-496.
⁴VON JAKSCH, R.: Multiple Periostaffection

- und an myelogene Leukämie mahnender Blutbefund, *Prag. med. Wchnschr.*, 1901, xxvi, 19-23.
- ⁵ASKANAZY, M.: Über extrauterine Bildung von Blutzellen in der Leber, *Verhandl. d. deutsch. path. Gesellsch.*, 1904, vii, 58-65.
- ⁶NAUWERCK, C., and MORITZ, P.: Atypische Leukämie mit Osteosklerose, *Deutsch. Arch. f. klin. Med.*, 1905, lxxxiv, 558.
- ⁷ASSMANN, H.: Beiträge zur osteosklerotischen Anämie, *Beitr. z. path. Anat. u. z. allg. Path.*, 1907, xli, 565-595.
- ⁸LEHNDORFF, H., and ZAK, E.: Myeloide Leukämie im Greisenalter mit eigenartigen histologischen Befunden, *Folia haematol.*, 1907, iv, 636-652.
- ⁹GOODALL, A.: Acute myelocythaemia associated with osteosclerosis and other unusual features occurring in an infant, *Edinburgh Med. Jr.*, 1912, viii, 500-507.
- ¹⁰DIEL, P., and LEVY, M.: Beitrag zum Studium der aleukämischen Myelose, *Ztschr. f. klin. Med.*, 1918, lxxxvi, 139-147.
- ¹¹LAURELL, H., and WALLGREN, A.: Untersuchungen über einen Fall einer eigenartigen Skeletterkrankung (Osteosclerosis fragilis generalisata), *Upsala Läkaref. Förh.*, 1920, xxv, 309-340.
- ¹²OESTERLIN, E.: Ein Fall kombinierter Knochen-Bluterkrankung, *Virchow's Arch. f. path. Anat.*, 1923-24, 589-598.
- ¹³NADOLNY, G.: Diffuse Osteosklerose im Kindesalter, *Jahrb. f. Kinderh.*, 1924, lv, 212-222.
- ¹⁴KRAUS, E. J., and WALTER, A.: Zur Kenntnis der Albers-Schönbergschen Krankheit, *Med. Klin.*, 1925, xxi, 19-22.
- ¹⁵BERNHARDT, H.: Ein Beitrag zur Marmor-knochenkrankung (Albers-Schönbergsche Krankheit), *Klin. Wchnschr.*, 1926, v, 415-417.
- ¹⁶HAGEDORN, K.: Über einen Fall aleukämischer Myelose mit Osteosklerose und einer alten Gicht, *Beitrag zur Frage der aleukämischen Myelose, ihren Beziehungen zur perniziösen Anämie und zur Osteosklerose und des Problems Gicht und Leukämie*, *Ztschr. f. klin. Med.*, 1926, civ, 124-149.
- ¹⁷REICH, F.: Aleukämische Myelose und Osteosklerose, *Med. Klin.*, 1927, xxiii, 143-147.
- ¹⁸JORES, A.: Ein Fall von aleukämischer Myelose mit Osteosklerose des gesamten Skelettsystems, *Virchow's Arch. f. path. Anat.*, 1927, cclxv, 845-851.
- ¹⁹MAVROS, A.: Aleukämische, besser "nicht-leukämische" Myelose mit Osteosklerose, *Folia haemat.*, 1931, xliii, 323-339.
- ²⁰SCHWARZ, E.: Ein Fall von Leukämie mit Riesenzellenembolie und allgemeiner Osteosklerose, *Ztschr. f. Heilk.*, Abth. f. path. Anat., 1901, xxii, 294-333.
- ²¹BAUMGARTEN, P.: Myelogene Pseudoleukämie mit Ausgang in allgemeine Osteosklerose, *Arb. a. d. Geb. d. path. anat. Inst. zu Tübingen*, 1899, ii, 499.
- ²²SCHMORL, F.: Leukämie mit Ausgang in Osteosklerose, *Münch. med. Wchnschr.*, 1904, li, 537.
- ²³PASTORE, S.: Pseudoleucemia e osteosclerosi, *Policlinico*, 1922, xxix, sez. med., 595-609.
- ²⁴REICHE, F.: Osteosklerose und Anämie, *Münch. med. Wchnschr.*, 1915, lxii, 944-946.
- ²⁵LOREY, A., and REYE, D.: Über Marmor-knochen (Albers-Schönbergsche Krankheit), *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1923, xxx, 35-43.
- ²⁶ZYPKIN, S. M.: Ein Fall von lymphatischer Pseudoleukämie mit Osteosklerose und Ausgang in akute lymphatische Leukämie, *Folia haemat.*, 1927, xxxv, 7-20.
- ²⁷DOAN, C. A.: Clinical implications of experimental hematology, *Medicine*, 1931, x, 323-371.
- ²⁸MOTT, F. W.: A case of spleno-medullary leukemia with hemorrhage into the cochlea and semicircular canals, associated with deafness and loss of balance, *Med.-Chir. Trans.*, 1900, lxxxiii, 209-219.
- ²⁹DONHAUSER, J. L.: The human spleen as an hematoplastic organ, as exemplified in a case of splenomegaly with sclerosis of the bone-marrow, *Jr. Exper. Med.*, 1908, x, 559-574.
- ³⁰WEBER, F. P.: A case of osteosclerotic anemia or leukemia, *Med. Press and Circular*, 1929, cxxvii, 75.
- ³¹WEBER, F. P.: Specimens from a case of osteosclerotic anemia or leukemia (miliary carcinomatosis), *Tr. Med. Soc. London*, 1929, lii, 99-103.

Some Unusual Cardiac Complications of Hyperthyroidism*†

A Report of Four Cases

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OCCASIONALLY we encounter patients with heart disease who have none of the usual etiological or associated diseases, viz., hypertension, the rheumatic syndrome, or lues. Obscure hyperthyroidism must be excluded in these cases. Since 1924 there have been numerous publications on hyperthyroidism masked as heart disease. Levine and Walker¹ recently reviewed the literature and reported eleven such cases.

Thyrotoxicosis imposes a tremendous burden on the heart. Even with the patient at rest the work of the heart in an individual with hyperthyroidism is comparable to that of the normal heart when undergoing the most strenuous exercise.² If this over-activity is continued for any great length of time, widespread myocardial damage may result. Following thyroidectomy the work and volume output of the heart returns to normal³ and there is a striking increase in myocardial reserve. Thyroidectomy should be attempted even in patients

with advanced myocardial failure after proper medical preparation.

DIAGNOSIS

To suspect thyrotoxicosis in the absence of physical signs is essential in making a diagnosis in these obscure cases. Attempts should be made to elicit a history of nervousness, palpitation of the heart, loss of weight, diarrhea of inexplicable origin, excessive sweating, premature gray hair, the preference of cold to hot weather, and the familial occurrence of hyperthyroidism. On close questioning a history of hyperthyroidism with a spontaneous remission many years before may be obtained.

On examination a slight general increase in excitability of the patient may be encountered. The skin often assumes a "salmon-like" hue and is warm, moist, and velvety. The hair may be prematurely gray. The thyroid gland may or may not be palpable. The heart is usually enlarged. The apical first sound is usually accentuated. There is often a systolic murmur at the apex. On one occasion the authors found a diastolic murmur over the aortic area with all the accompany-

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ing signs of aortic insufficiency, which disappeared following operation. There is usually an elevation of the systolic pressure and an increase of pulse pressures. The heart rate is usually rapid and the rhythm is often irregular. In one patient, in the series reported below, an electrocardiogram showed the arrhythmia to be due to auricular fibrillation and in another to auricular premature beats.

Occasionally thyrotoxicosis may manifest itself principally as precordial pain, and we may find coexisting coronary disease and hyperthyroidism. Lev and Hamburger³ have reported such a case. Unusually severe and frequent attacks of precordial pain in patients without the usual signs of accompanying vascular disease should arouse the suspicion of thyrotoxicosis as an etiological or contributing factor.

When suspected, the diagnosis can be confirmed or ruled out by basal metabolism tests. Elevated metabolic rates are sometimes associated with cardiac failure, but this increase is usually not more than 20 per cent.⁴ Repeated tests should be made on those patients in whom hyperthyroidism is suspected and if these are not conclusive the therapeutic iodine test may be done. In the cases reported below the metabolic readings were quite conclusive as they were \pm 40 per cent or more on repeated determinations. The finding of a relative lymphocytosis, which has been observed in a large percentage of patients with hyperthyroidism, may be of some diagnostic aid.^{5,6}

After corroboration of the diagnosis a very careful examination of the

heart and a teleoroentgenogram and electrocardiogram should be made to determine the extent of the cardiac damage.

MANAGEMENT

Since the introduction of iodine for the preoperative preparation of patients with hyperthyroidism its misuse has increased yearly in spite of frequent publications on this subject. Iodine should almost never be given unless plans for operation have been made. The administration of iodine is generally followed by a period of improvement lasting several weeks. If operation is not performed during this period of improvement the iodine effect is lost and a relapse will occur. Relapses are often accompanied by violent "thyroid storms". If a "storm" occurs in a patient with an already seriously damaged myocardium, death may result. If the patient survives the "storm" and operation is attempted, the surgeon is at a great disadvantage since the patient is usually refractory to iodine for several weeks. Operation without the use of iodine, especially in a patient with heart disease, is a hazardous undertaking.

It is sometimes difficult to find a surgeon who will agree to operate on a patient with cardiac failure even though he is convinced that the etiology is hyperthyroidism. When the diagnosis has been based upon a careful study, and when adequate preoperative preparation can be carried out, we feel that internists should strongly urge the performance of thyroidectomy.

The use of digitalis is frequently discouraging in patients with hyper-

thyroidism. It is a well-known fact that this drug will often fail to slow the heart rate in a patient with auricular fibrillation when the auricular fibrillation is associated with thyrotoxicosis. Probably the only indication for digitalis in thyroid heart disease is the presence of congestive heart failure. It is usually unnecessary to treat auricular fibrillation with quinidine as the majority will revert to normal rhythm after thyroidectomy.

Preoperative preparation should consist of complete bed rest, forced feedings, and large doses of sedatives. After consent for operation has been obtained, iodine may be begun. Basal metabolic rates should be determined at intervals of four or five days. After ten to fourteen days of iodine administration the patient's general condition will usually be much improved and the metabolic rate greatly reduced. Operation can then be performed without difficulty.

Instances arise in which patients with hyperthyroidism have to be treated without operation. This is at present a long and often disappointing procedure. Absolute bed rest with forced feedings and large doses of sedatives must be insisted upon. Marine⁷ has suggested the use of iodine in very minute doses, 1 milligram (or 1/60 grain) three times daily over an extended period of time. This produces a more gradual reduction in thyroid overactivity, and "iodine escape" with its attendant evils is less likely to occur. The use of ergotamine tartrate has been advocated by some⁸ as an aid in reducing the metabolic rate because of its depressive action on the

sympathetic nerve system. The recent work of Youmans and Trimble⁹ seems to indicate, however, that this drug is without value in the treatment of hyperthyroidism.

Radiation of the thyroid gland was used rather extensively in the medical treatment of hyperthyroidism a few years ago. This procedure also has proved unsatisfactory; it has the added disadvantage of making the gland quite difficult to remove if surgery is attempted at some later date.

CASE I

Mrs. D. H. W., a Caucasian housewife of 46 years, was first admitted to the hospital June 20, 1931, complaining of nervousness, palpitation of the heart, shortness of breath and loss of weight.

Five months before admission she consulted her family physician because of occipital headaches. She was referred to a dentist who found several abscessed teeth. These were removed and the headaches disappeared. A short time later she first noticed a rapid and forceful heart action with shortness of breath on slight exertion. She was extremely nervous and easily fatigued. She was also losing weight in spite of a very good appetite. Three months after the onset of the present illness the shortness of breath had become quite marked and she first noticed swelling of the feet and ankles. Upon the advice of her family physician she went to a hospital. There she was given Lugol's solution for about two weeks and showed marked improvement. She was then discharged from the hospital but remained in bed at home. There was a return of symptoms in about six weeks and she was seen by us at that time.

Her past history was unimportant except for occasional attacks of diarrhea all of her life. She admitted a preference for cold weather; and she had noted an increase in nervousness during the past three years.

On examination she was an emaciated, anemic, dyspneic, generally overactive, middle-aged woman lying propped up in bed.

The skin was warm, velvety, and had a "salmon yellow" tint. The hair was gray. The eyes were blue. There was well marked lid-lag and exophthalmos. The conjunctivae and the mucous membranes of the mouth were quite pale. The small papillae of the tongue were atrophied. The thyroid gland was soft and symmetrically enlarged. There was a definite thrill and bruit present. There was marked over-filling of the jugular veins and the carotid pulsations were vigorous. A moderate number of medium moist râles was found at the bases of both lungs. The apex impulse of the heart was diffuse and forceful. There was a moderate cardiac hypertrophy; the left border of dullness was 11.5 cm. from the midline, the right border 5 cm., and the supracardiac dullness in the second interspace was 7 cm. in width. The first sound at the apex was greatly accentuated and there was a loud systolic murmur. At the left sternal border in the fourth intercostal space there was a long high-pitched diastolic murmur. This was also heard over the second right interspace. The aortic second sound was audible but muffled. The heart rhythm was fundamentally regular but there were frequent premature beats. The rate was 100 per minute. The entire vascular bed was shaken with each systole. All peripheral veins pulsated. There was a Corrigan pulse, and pistol shot sounds were heard over the femoral vessels. The blood pressure was 160 mm. Hg systolic and 0 mm. diastolic. There was a moderate pitting edema of the ankles and slight edema in the sacral region.

The blood count showed 3,000,000 red cells and the hemoglobin was 50 per cent (Dare). There was 39 per cent of lymphocytes in the blood smear. The reticulocyte count was 2.8 per cent. The blood chemical tests performed gave normal results and the Wassermann reaction was negative. The urine examination was negative, and there was a phthalein excretion of 82 per cent in two hours. The basal metabolic rate on admission was $+38$ per cent. The electrocardiogram showed a biphasic "T" wave and slight notching and slurring of the "Q-R-S" complex in lead I. There were numerous auricular premature beats. The gastric analysis

showed a total acidity of 67 degrees with 28 degrees of free hydrochloric acid.

The patient was given her calculated dose of digitalis, heavy doses of bromides, and 5 drops three times daily of Lugol's solution. The secondary anemia was treated with preparations of liver and of iron. Two transfusions were given. Two weeks after admission the cardiac failure had largely subsided, the blood pressure was 140 mm. Hg systolic and 40 mm. diastolic. The peripheral signs of aortic insufficiency and the diastolic murmur were still present.

Three weeks after admission the blood count was practically normal and all signs of cardiac failure had disappeared. The basal metabolic rate was $+38$ per cent. A subtotal thyroidectomy was done at this time. The postoperative course was not unusually severe but probably more so than if iodine had not been given previous to her preoperative preparation. There was a moderate tracheitis. The temperature was 100 degrees for two or three days. Convalescence was uneventful and she was discharged ten days after operation.

One month after operation the patient had gained 16 pounds in weight and felt quite well. Her only symptoms were occasional palpitation of the heart and easy fatigue. There were no signs of cardiac failure. The over-activity of the heart had completely disappeared and the diastolic murmur and peripheral signs of aortic insufficiency were no longer present. The blood pressure was 145 mm. Hg systolic and 70 mm. diastolic. There was a moderate systolic murmur at the apex, the heart rate was 66 per minute and the rhythm completely regular. The basal metabolic rate was $+3$ per cent. The blood count and urinalysis were normal.

DISCUSSION

This patient illustrates the importance of making an early diagnosis and removing the thyroid gland before cardiac damage has become so advanced. The necessity of operating, even though there is advanced heart failure, is also well demonstrated. This patient had a striking return of circulatory competence in spite of the fact that her degree of congestive heart failure was advanced. It was with some difficulty that the

surgeon was convinced that she did not have primary heart disease with aortic insufficiency. There is nearly always an increase in pulse pressure with thyrotoxicosis because of the increased amount of blood that is discharged from the ventricles with each systole. Only very rarely, however, will it produce the peripheral signs of an aortic insufficiency. These signs, associated with the diastolic murmur, made the picture quite confusing. The cause of the diastolic murmur was uncertain. A combination of the anemia and hyperthyroidism may have been responsible.

Anemia is a very unusual complication of hyperthyroidism. There is often an increase in the red cell count. This patient's anemia was of a secondary type but its cause remained obscure, as her diet had been unusually adequate and there was no history of blood loss or of chronic infection.

CASE II

L. S., a colored male cook of 51 years, was admitted to the hospital April 6, 1931, operated on June 6, 1931, and died twenty-four hours later.

Seven months before admission the patient began to have diarrhea. There were no abdominal cramps and no blood or mucus in the stools. At first there were two to four stools daily; these later increased to six or eight and he became quite weak. Associated with the diarrhea there was occasional epigastric fullness, palpitation of the heart, and shortness of breath. He lost 27 pounds during the seven months prior to admission to the hospital. The appetite was fair during this time and his diet was not particularly lacking in any of the essential foods. He had noticed very little increase in nervousness.

The past history was unimportant except for a period of diarrhea twenty-six years before. He had gray hair at the age of thirty and premature grayness was a paternal hereditary trait.

On examination he was lying quietly in bed, without apparent nervousness or over-activity. The skin was warm, moist and velvety. There was no lid-lag, exophthalmos or loss of convergence. There was moderate retinal sclerosis. The tongue

showed an unusual redness, and there was some atrophy of the small papillae. The thyroid was not felt but there was some fixation of the trachea. The lungs were normal. The apex impulse of the heart was rather forceful in the fifth interspace just outside the midclavicular line. The heart was moderately enlarged to percussion. The left border of dullness measured 10 cm. from the midline, the right border 3 cm., and the supracardiac dullness in the second interspace was 5 cm. in width. Over the apex there was some accentuation of the first sound and a soft systolic murmur. The aortic second sound was of fair quality and greater than the pulmonic second sound. No diastolic murmurs were heard at this time. The heart rate was 120 per minute and the rhythm regular. The blood pressure was 135 mm. Hg systolic and 70 mm. diastolic. There was slight sclerosis of the radial vessels. The abdomen was emaciated but there was no tenderness or enlargement of organs. There was no edema of the feet and ankles. The extended fingers showed a moderate fine tremor. There was some pallor of the nails and of the mucous membranes. The reflexes were normal.

Examination of the blood showed 3,000,000 red blood cells with a hemoglobin of 55 per cent. There was a lymphocytosis of 59 per cent. The reticulocyte count was .7 per cent. The urine examination was entirely normal. The Wassermann test was negative. Repeated blood cultures were negative. Examination and culture of the stool revealed nothing unusual. The gastric analysis showed no free hydrochloric acid and a combined acidity of only two degrees. The duodenal contents were normal. Roentgenographic examination of the gastrointestinal tract showed only some spasticity of the descending colon.

During the early part of his stay in the hospital efforts were directed largely towards finding an explanation for the diarrhea, the achlorhydria, the anemia, the papillary atrophy of the tongue and the premature gray hair. The vascular findings were regarded as secondary to the long-standing diarrhea and anemia. The diagnostic possibilities were numerous and included

pellagra, sprue, primary anemia, and chronic ulcerative colitis.

Eleven days after admission the heart rhythm became grossly irregular and the electrocardiogram showed the presence of auricular fibrillation. A pulse deficit of twenty per minute was associated with the arrhythmia. After the onset of auricular fibrillation the possibility of hyperthyroidism as an explanation for the entire clinical picture was considered. The basal metabolic rate was determined on three successive occasions and found successively to be +47, +32, and +36 per cent.

During the next month the treatment consisted of forced feeding and the administration of sedatives and preparations of liver and iron. He continued to lose weight and there was no increase in the red blood cells or hemoglobin. Auricular fibrillation continued and a diastolic murmur developed over the second right interspace at the sternal border. There was no decrease in the diastolic pressure. The patient was advised to have the thyroid removed and he finally consented. Lugol's solution was begun and the metabolic rate dropped to +10 per cent during the next two weeks but with very little improvement in his general condition.

Two months after admission, and two weeks after beginning iodine, a subtotal thyroidectomy was performed. A few hours later the patient's temperature rose to 106 degrees F. The heart rate was 150 per minute, and the rhythm grossly irregular. He was treated with oxygen and the usual supportive measures but failed to rally, and died thirty-six hours after operation.

DISCUSSION

This patient presented a most difficult diagnostic and therapeutic problem. The thyroid overactivity may have been primarily responsible for the entire picture, but the course of events makes one suspect that it was associated with a "pellagra-like" deficiency disease. We believe that this case affords a striking example of the close association of these diseases with hyperthyroidism. The symptoms of cardiovascular disease were not permanent and it was only after the development of auricular fibrillation that attention

was focused on them. The lack of improvement after the administration of Lugol's solution, in spite of a drop in the metabolic rate, further emphasizes the probability of an association of diseases rather than just an unusual and obscure hyperthyroidism.

CASE III

L. B. S., a colored maid of 56 years, was first admitted to the hospital September 15, 1930, operated on January 28, 1931, and discharged February 5, 1931.

About the time of puberty this patient first noticed a slight enlargement of the thyroid gland. This enlargement persisted but without symptoms or change in size throughout the years that followed. Two months before admission to the hospital she first noticed slight palpitation of the heart and shortness of breath on exertion. She also noticed a fullness beneath the sternum but no pain. There was no nervousness, no increase in appetite and no loss in weight.

On examination at this time there was no general overactivity nor any signs to suggest thyrotoxicosis. There was a small nodular enlargement of the thyroid without thrill or bruit. The eye signs of hyperthyroidism were absent. The skin, while moist and velvety, was cooler than normal. There was no significant tremor.

The heart was moderately enlarged and there was a palpable thrill over the base. The apical first sound was somewhat accentuated and there was a long, harsh systolic murmur in this area. Over the second right intercostal space there was a long, high-pitched systolic murmur which was transmitted into the vessels of the neck, and a shorter and lower pitched diastolic murmur. This was better heard in the left intercostal spaces at the sternal border. The aortic second sound was not heard. The rhythm was regular. The rate was 80 per minute. There was a moderate sclerosis of the radial and retinal vessels. Moist râles were present at the bases of both lungs. The blood pressure was 240 mm. Hg systolic and 130 mm. diastolic. The abdomen was essentially negative. There was slight pitting edema over the tibiae. The height was 5 feet, 4 inches, and the weight 138 pounds.

Examination of the urine showed nothing unusual. The phthalein excretion was 55 per cent in two hours. The blood count was normal except for a lymphocytosis of 50 per cent. The Wassermann test was negative. The blood chemical tests gave normal results. A teleoroentgenogram of the heart showed the aortic shadow to be 5.5 cm. in width; the right margin 5 cm., and the left margin 10.5 cm. from the midline. The electrocardiogram showed only a left axis deviation. The vital capacity was 3 liters.

From this study it was concluded that the patient had hypertensive heart disease and early congestive heart failure. The auscultatory findings over the aortic area were difficult to explain on a rheumatic or luetic basis and it was thought that they might be due to calcareous deposits on the aortic cusps.

The patient was treated by bed rest, digitalis, and sedatives but with very little evidence of improvement. It was then decided to determine the basal metabolic rate because of the nodule in the thyroid gland. The rate was found to be + 51 per cent in the first test and + 55 per cent in a second test a few days later. The patient was advised to enter the hospital for thyroidectomy but refused. She remained in bed at home and was given digitalis, bromides, and forced feedings. Even with the above treatment she lost weight and showed no improvement except for the disappearance of the symptoms of cardiac failure.

Three months later she consented to operation. After two weeks of preparation with iodine she was generally improved; a subtotal thyroidectomy was done without difficulty. The postoperative course was uneventful except for a drop in blood pressure to 140 mm. Hg systolic and 80 mm. diastolic. One month after operation the patient had gained 20 pounds in weight and felt quite well. The blood pressure had increased to 170 mm. Hg systolic and 90 mm. diastolic. She has been seen at regular intervals for about one year. There has been no return of congestive heart failure. She has gained 25 pounds. The basal metabolism is normal. The blood pressure has gradually increased to 190 mm. Hg systolic and 90 mm. diastolic. The auscultatory signs of the heart are unchanged.

DISCUSSION

The relation of the nodular thyroid gland to the hypertensive heart disease is of interest in this patient. The thyrotoxicosis may have been a longstanding, recurring one without symptoms but with the gradual production of vascular damage. The hypertensive vascular disease may have developed without relation to the goiter. The nodular thyroid, after years of latency, may have recently become toxic, and, superimposed on an already damaged vascular system, may have caused cardiac failure. The diastolic murmur did not disappear following operation. Its etiology still remains obscure.

In the absence of the usual signs thyrotoxicosis would not have been even suspected if the nodular thyroid had not suggested this possibility. The removal of the burden of an increased metabolism has considerably increased the patient's cardiac reserve so that she may, with proper care, live for several years.

CASE IV

Mrs. I. Q., a housewife of 47 years, was admitted to the hospital July 3, 1931, complaining only of weakness and occasional palpitation of the heart. This was first noticed about two weeks before admission. Previous to this time there had never been any complaints referable to the heart except for occasional "fluttering" on going up stairs. She had never been excessively nervous. There was no history of digestive disturbance and her appetite had been good until recently. There had been no recent loss in weight.

On physical examination she was a well developed and well nourished Jewish woman lying quietly in bed. There was no general overactivity. The skin was moist but not particularly warm or soft. There was a beginning arcus senilis. There was no lid-lag, no exophthalmus and no failure of convergence. Fundus examination showed slight sclerosis of the retinal arteries. All teeth had been removed. The tongue protruded normally. The thyroid was not enlarged. There were no thrills, no bruits, and no unusual pulsations in the neck. The chest was symmetrical, expansion fair, and the lungs were clear throughout. The apex

impulse of the heart was felt in the fifth intercostal space 9 cm. from the midsternal line. By percussion the heart was found slightly enlarged, measuring 3 cm. to the right of the midline and 9.5 cm. to the left. The supracardiac dullness was 5 cm. in width. The first sound at the apex was a little distant and of inferior quality. There was a soft systolic murmur. The aortic and pulmonic second sounds were equal, and both were of fair quality. No diastolic murmurs were heard. The heart rate was 80 per minute. The rhythm was grossly irregular but there was no pulse deficit. There was a slight sclerosis of the radial vessels. The blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. The abdomen was not unusual. The extremities showed slight pitting edema. There was no tremor of the extended fingers.

The blood count was normal. The urine examination was negative. The electrocardiogram showed auricular fibrillation with normal ventricular complexes. A basal metabolic rate was determined and found to be + 50 per cent. A second test was similar to the first.

After the metabolic rates were determined the patient was told that she had hyperthyroidism and operation was advised. She elected to defer removal of the gland and to take a period of bed rest with sedatives and forced feedings. The basal metabolic rate had decreased to + 19 per cent after five weeks of this treatment but there was some increase in the heart rate, and a pulse deficit of 10 to 15 per minute had developed. This could be eliminated by the use of digitalis.

DISCUSSION

Auricular fibrillation is usually associated either with hypertensive heart disease, with mitral stenosis or with hyperthyroidism. In

this patient there was very little evidence of vascular disease. The blood pressure was normal and there was only slight sclerosis of the vessels. There were no signs of mitral stenosis. In the absence of these two most frequent coexisting diseases (mitral stenosis and hypertensive vascular disease), hyperthyroidism was suspected as the etiological factor of her auricular fibrillation even though there were no clinical signs of its presence.

This patient's prognosis depends entirely on whether or not the thyroid overactivity will subside without operation. There is already considerable myocardial damage and she will probably develop an advanced congestive heart failure if the cardiac burden persists. As digitalis controls the pulse deficit and the heart rate, it was deemed unnecessary to attempt to obtain a normal rhythm through the use of quinidine.

This patient illustrates the importance of suspecting thyrotoxicosis in individuals who have an obscure type of auricular fibrillation even in the absence of any physical signs.

SUMMARY

1. Four patients with hyperthyroidism and unusual cardiac complications are presented and discussed.
2. The necessity of suspecting hyperthyroidism in some patients with heart disease, even though there are none of the usual signs of thyrotoxicosis, has been illustrated.
3. The diagnosis and treatment of patients with hyperthyroidism and unusual cardiac complications have been outlined.

BIBLIOGRAPHY

- LEVINE, S. A., and WALKER, G. L.: Further observations on latent hyperthyroidism masked as heart disease; angina pectoris, *New England Jr. Med.*, 1929, cci, 1621-1630.
- REDFERN, C. S., SMITH, W. C., and NEIGH-

- BORS, DEW.: Output of heart in thyrotoxicosis, with report of case of thyrotoxicosis combined with primary pernicious anemia, *Am. Jr. Med. Sci.*, 1929, clxxviii, 157-168.
- LEV, M. W., and HAMBURGER, W. W.: As-

sociation of angina pectoris and hyperthyroidism, *Am. Heart Jr.*, 1928, iii, 672-681.

⁴PEABODY, F. W., WENTWORTH, J. A., and BARKER, B. I.: Clinical studies on the respiration. V. The basal metabolism and the minute-volume of the respiration of patients with cardiac disease, *Arch. Int. Med.*, 1917, xx, 468-478.

⁵PLUMMER, W. A.: The blood picture in exophthalmic goiter, *Minnesota Med.*, St. Paul, 1919, ii, 330-332.

⁶MENKIN, V.: Relative lymphocytosis in hyperthyroidism, *Arch. Int. Med.*, 1928, xlii, 419-424.

⁷MARINE, D.: Iodine in treatment of diseases of the thyroid gland, *Medicine*, 1927, vi, 127-141.

⁸ADLERSBERG, D., and PORGES, O.: Über die Behandlung des Morbus Basedow mit Ergotamin (Gynergen), *Klin. Wchnschr.*, Berl., 1925, iv, 1489-1493.

⁹YOUNG, J. B., and TRIMBLE, W. H.: Experimental and clinical studies of ergotamine; effect of ergotamine on basal metabolism, circulation and blood sugar of normal persons and of patients with thyrotoxicosis, *Arch. Int. Med.*, 1931, xlvii, 612-632.

Pneumosilicosis and Amyloidosis*†

Report of a Case of Asymptomatic Pulmonary Silicosis and Amyloid Kidney; Death from Uremia.

By J. B. CAREY, M.D., F.A.C.P., *Minneapolis, Minnesota*

THE condition of pneumosilicosis is in itself of interest only as an occupational disease. Its gradual production by intermittent rather than by constant exposure to silica-bearing dust, without apparent symptoms and with no accompanying infection, may perhaps be unusual. The deposition of silica-bearing particles of foreign material in the lung, causes much fibrosis. That this fibrosis is the direct result of irritation by the silica itself, and not of simple mechanical traumatization of pulmonary tissue by a foreign agent as such, is conceded. In individuals in whose lungs silica has been deposited, symptoms apparently result from the secondary infections which occur in such irritated organs. That the silica or any compounds derived from it may cause systemic symptoms or metastatic effects is not apparent from our present knowledge.

The association, in the same individual, of a condition of pulmonary silicosis and renal and splenic amyloidosis has not, to the author's knowledge, been reported. Because of such

a bizarre coincidence—one hesitates to call it a relationship—the following case is detailed. There is the further unusual circumstance that the amyloidosis of the kidney resulted in a renal impairment, progressive to the point of causing the death of the patient in uremia.

CASE REPORT

A white male, 49 years of age, was brought into the clinic December 9, 1931, complaining of weakness and diarrhea. In addition to his regular occupation as a farmer, the patient, for the past 21 years, had occasionally worked in granite yards and quarries for considerable periods at a time. The intermittent periodicity of this labor seems important. He was an only child. His father had died at the age of 82, but his mother was still living at 88. He was married and had six children, all living and well.

The patient had never had any illness or disability which interfered with his work until the onset of the present symptoms. The only illness of note in his past history was an attack of "bronchitis" in the fall of 1930 which did not incapacitate him.

On October 22, 1931, a large block of granite, on which the patient was working in a stone-cutting yard, slipped from its supports and fell over against him, striking him across the abdomen and knocking him down. He was thus thrown upon a smaller block, so as to be struck across his left back. He was not rendered unconscious by

*Read before the Minnesota Society of Internal Medicine, June 4, 1932.

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this injury nor did he show signs of shock or hemorrhage at that time. He was placed in a hospital in St. Cloud, Minnesota, and remained there until November 14, 1931. During his stay in the hospital he suffered from backache, became very weak and lost weight. Diarrhea developed and persisted. When he finally went home the backache was less troublesome but the other symptoms continued. He was finally brought to the clinic by his daughter on the date mentioned.

There was no further history elicited. His complaints were weakness, diarrhea, weight loss, anorexia, and pain in the left back and side. The man seemed quite ill and unable to move about comfortably. He was therefore immediately placed in the hospital.

A résumé of the pertinent findings discovered in the subsequent examination is tabulated as follows:

Skin: pale, sweaty.

Pulse: 100.

Blood pressure: 100/60 mm. Hg.

Eye-grounds: negative.

Heart: normal.

Lungs: negative on physical examination.

Abdomen: slight tenderness deep in left upper quadrant (spleen not palpable).

Back: tenderness of lumbar muscles of left side, but no abnormality of spine itself, discovered; no edema.

Extremities: no edema.

Neurological examination: negative.

Blood: Hgb. 72 (Sahli).

R.B.C. 4,010,000.

W.B.C. 8,700—P.M.N.'s 72, lymphocytes 25, eosinophiles 3.

N.P.N. 50.8 mg. per 100 c.c.

Urine: Sp. gr. 1.018.

Albumin 2+.

Sugar 0.

Hyaline and granular casts, occasional R.B.C. and 8-12 pus cells per high power field.

Dilution and concentration test: fixation of sp. gr. 1.009-1.012.

Fixation of amount 50-70 c.c. per hour.

Phthalein: 20% first hour, 25% second hour.

Gastric Contents (45 min., after Ewald meal): Free HCl 0.

Combined acid 12.

Roentgenological studies:

Kidney, ureter and bladder regions: negative.

Spine: moderate hypertrophic changes.

Lungs: pneumosilicosis (Figure 1).

Stomach and bowel: negative.

Cystoscopic examination with pyelograms: opinion, bilateral pyelonephritis with

anatomical narrowing of ends of both ureters.

Urine obtained from ureteral catheterization:

Right: 20-30 pus cells per high power field, and a few r.b.c.

Left: 10-15 pus cells per high power field, and a few r.b.c.

Blood Wassermann: negative.

Clinical diagnosis:

Hypertrophic spinal arthritis (occupational).

Pneumosilicosis (occupational).

Sprain of back, traumatic, recovering.

Chronic nephritis, with moderate kidney insufficiency.

Chronic pyelitis, with moderate kidney insufficiency.

Achylia gastrica.

The patient remained in the hospital until December 24, 1931. Throughout his stay his pulse varied from 60 to 100, his temperature remained normal, and his blood pressure varied from 100 to 110 systolic and from 60 to 70 diastolic. Repeated examinations of urine specimens were made and always revealed variable amounts of albumin and numbers of pus cells, red blood cells, and hyaline and granular casts. He became quite comfortable while resting in bed. The diarrhea stopped, and the pain in the back was considerably improved. He was given dilute hydrochloric acid by mouth as this seemed to control his gastrointestinal symptoms. While in the hospital he was on a diet containing 60 gm. of protein.

After his discharge from the hospital he remained in the city, at the home of his daughter, where he continued the restricted diet and the use of dilute HCl, and reported for lavage of kidney pelvis and bladder at intervals. On January 26, 1932 he reported a recurrence of the diarrhea, possibly because he had stopped the use of the acid. He seemed somewhat paler on this date. A blood examination showed Hgb. 50 (Dare) R.B.C. 3,370,000. The urine showed albumin 4+ but no pus or blood cells.

Soon after this visit the patient went to his farm at Hinckley, Minnesota and remained there until he was brought into the hospital, on March 4, 1932, in a comatose condition. His wife said that he had contracted an upper respiratory tract infection about February 15 and that he had been bedridden since that time. There was not

versity of Minnesota. From his report the following facts were obtained:

The right lung weighed 1150 gm., the left 890 gm. The outer surfaces were of a greenish black mottled color. There was marked retraction by fibrosis toward the hilus in such a way as to produce lobulation. By palpation there was very little aerated tissue felt, except in the upper portion and periphery of the lung, most of the tissue being quite hard. The mediastinal nodes attached to the hilus were dark grayish in color and very hard. All of these findings were more marked in the right lung than in the left. The resistance to the cutting knife was harsh and gritty in character. On cut section the lung was found to be almost solid around the hilus, the normal tissue appar-

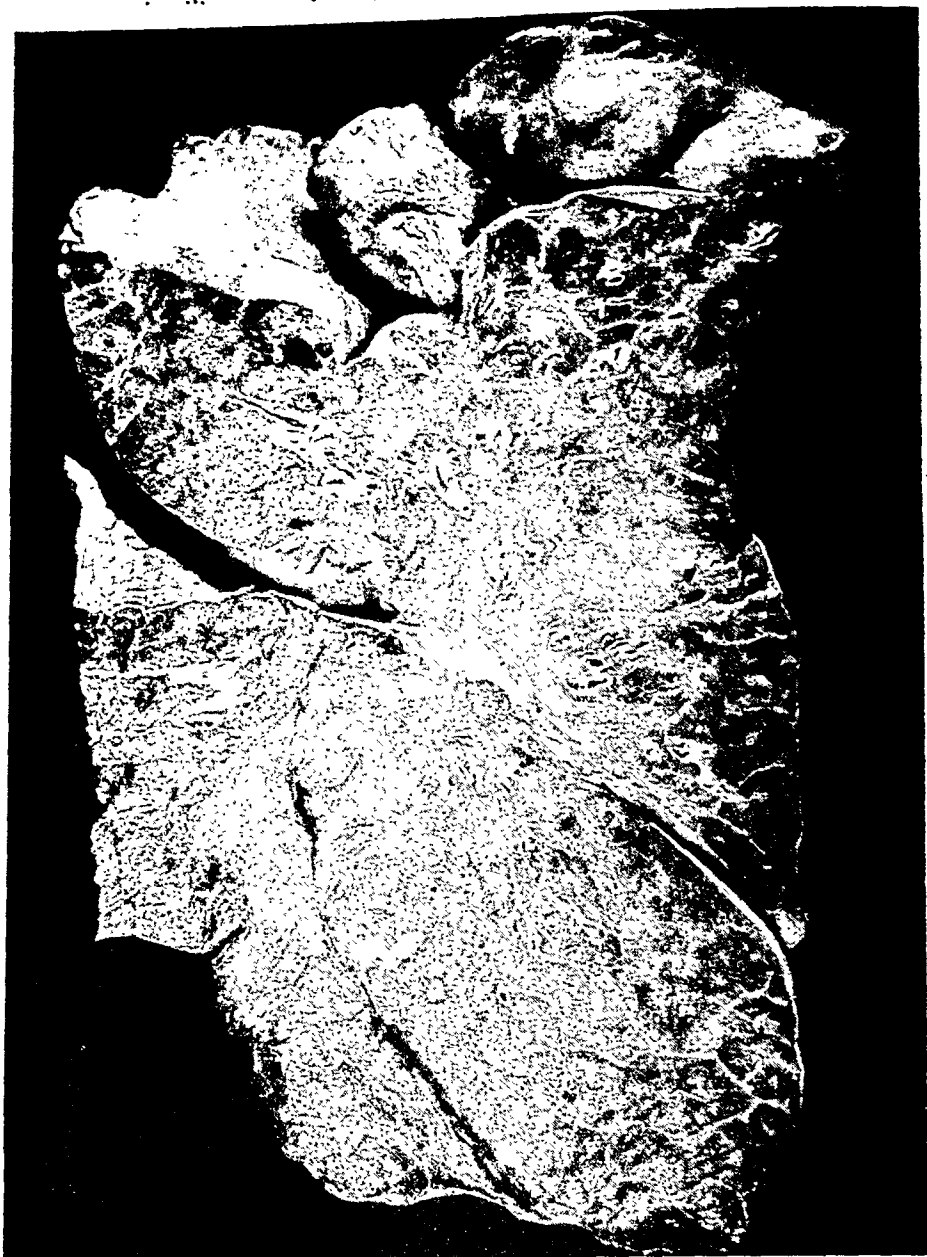


FIG. 2. Gross appearance of cut section of pneumosilicosis.

Blood pressure: 100/60 mm. Hg.
 Heart: negative except for rapidity of rate.
 Lungs: negative on physical examination.
 Bladder was catheterized and 200 c.c. of concentrated urine obtained showing a heavy trace of albumin, 1-2 hyaline casts, occasional r.b.c. and 4-5 pus cells.
 Blood: Hgb. 50 (Sahl).
 R.B.C. 3,600,000.
 Urea N. 95 mg. per 100 c.c.
 Creatinine 4.5 mg. per 100 c.c.
 CO_2 62 vol. %

Intravenous fluids were given which seemed to bring about a slight improvement in the general condition late in the afternoon. However, about 8:00 o'clock he sank into a deep coma from which he could not be aroused and died at 10:00 p.m.

An autopsy was performed the following morning at 9:30 o'clock by Dr. B. J. Pearson of the Department of Pathology, Uni-

much cough with this attack, but headache, malaise, fever, and a recurrence of the diarrhea had been noted. On February 20, without preceding symptoms, the right ear began to discharge. On March 2 the patient became stuporous and remained so until he was brought into the hospital two days later. During these two days he took no food and very little fluid and passed no urine.

The pertinent findings of an examination on March 4 were as follows:

Stuporous, semicomatose condition from which the patient could barely be aroused.

Skin: dry and pale.

No edema or ascites.

Reflexes: sluggish.

Eye-grounds: negative.

Respirations: rapid, but regular and of good amplitude.

Pulse: rapid, small volume, regular.



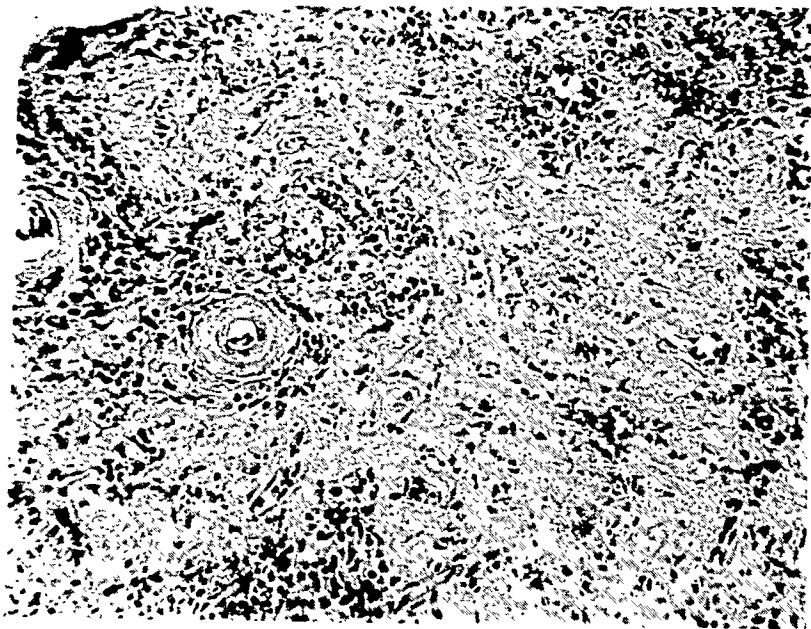


FIG. 4. Amyloid infiltration of spleen.

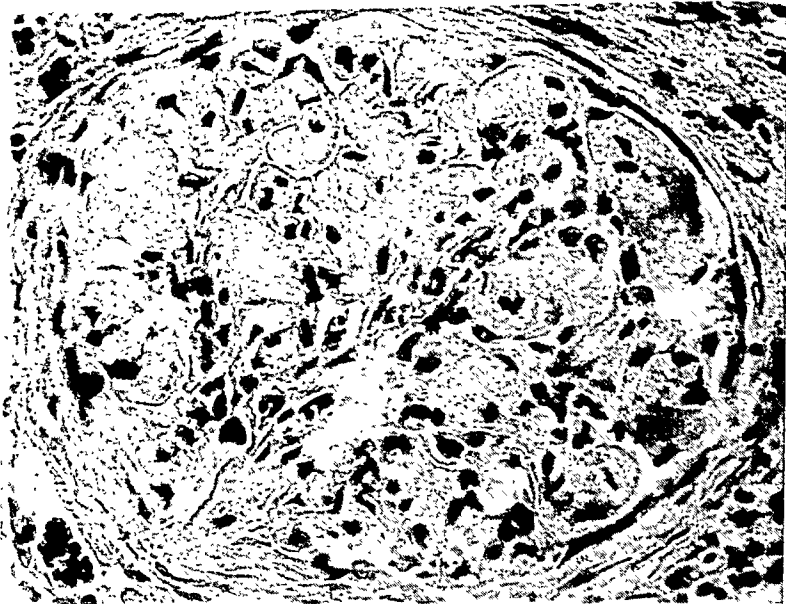


FIG. 5. Amyloid infiltration of glomerulus of kidney.

ently being almost completely replaced by the silica deposit. The resemblance of this substance to carborundum was striking. The hilus nodes cut like sandstone. This gritty material was present in other parts of the lung to a lesser extent than around the hilus, and in the left lung to a lesser degree than in the right. The extreme periphery was free from the substance. (Figure 2) Microscopic sections of lung tissue showed

showed amyloid infiltration replacing normal tissue to some extent. Otherwise nothing noteworthy was seen. (Figure 4)

The right *kidney* weighed 200 gm. and the left 225 gm. The capsules stripped easily and revealed smooth, pale, mottled surfaces of both kidneys. On cut section pale mottled areas were seen scattered throughout, predominating in the cortex. Although the texture was not typically that

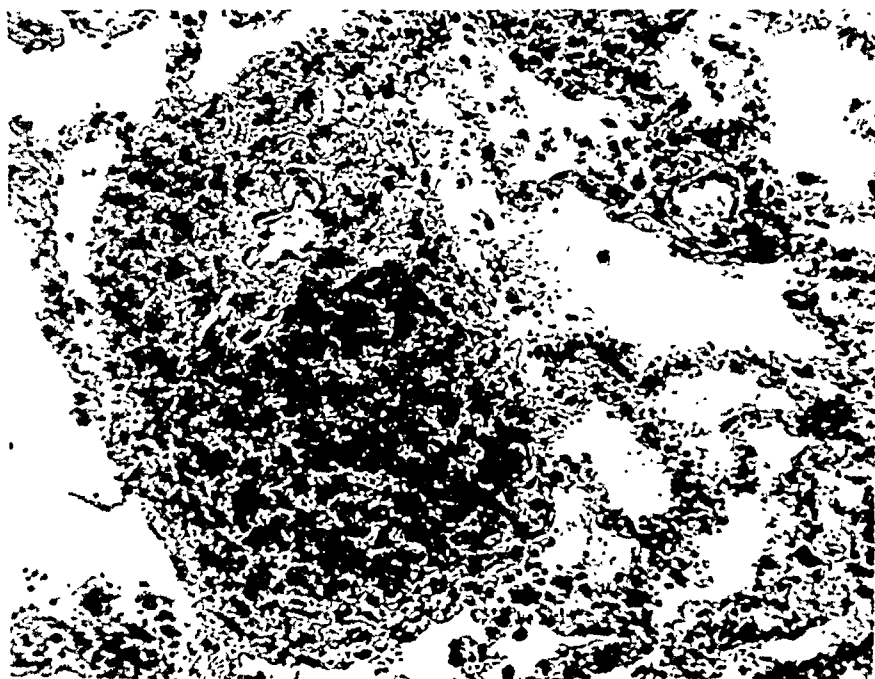


FIG. 3. Microscopic section of pneumosilicosis with fibrosis.

extensive deposit of silica and very marked fibrotic changes. There was no evidence of infection, tuberculous or otherwise. Figure 3 shows clearly the microscopic appearance of a typical area of pulmonary tissue.

The *heart* weighed 390 gm. There was very possibly a slight hypertrophy of the left ventricle. Slight coronary sclerosis was present and a few patches of sclerosis at the root of the aorta and near the aortic leaf of the mitral valve.

The *spleen* weighed 250 gm. It had a grayish, slightly wrinkled capsule. On cut section it was firm and presented a lardaceous texture interpreted as being due to amyloid infiltration. Tested grossly with iodine solution, amyloid stain was abundant and blue. Microscopic section of the spleen

of amyloid infiltration, staining with iodine showed this to be present abundantly. The kidneys showed no evidence of infection of the parenchyma or of the pelvis. Microscopic sections showed amyloid infiltration of the glomeruli with little or no amyloid in the tubular portion (figure 5), and none in the interstitial tissue.

The other organs were essentially negative. The *liver* weighed 2250 gm. and was grossly normal. On cut section it showed a moderate amount of cloudy swelling. There was no evidence of chronic passive congestion. The *gall-bladder* was quite distended with bile; but on careful dissection no obstruction was found.

The *stomach* was found to be normal. The *small and large intestines* showed no patho-

logical lesions. The *mesenteric glands* were normal in size and did not contain any silica deposit or amyloid. The abdominal glands were normal, except a few which were rather soft and dark. Microscopic examination of these glands was negative. The *pancreas* weighed 100 gm. and was normal grossly and on cut section. The *adrenals* seemed somewhat larger than normal, especially the left one. On cut section the proportion of cortex to medulla was normal and nothing unusual was noted. The *bladder* contained about 250 c.c. of cloudy urine. There was some hemorrhagic congestion of the mucosa. The *prostate* was of normal size. The *bones* of the thorax and spine were inspected and no evidence of injury was seen.

As before mentioned, all organs were tested for amyloid, and none was found except in the kidneys and spleen.

The complete anatomical diagnosis was:

- (1) Pneumoconiosis (silicosis),
- (2) Amyloid kidney,
- (3) Amyloid spleen,
- (4) Hydrothorax,
- (5) Pleural adhesions (right),
- (6) Diaphragmatic adhesions (left),
- (7) Cloudy swelling of liver,
- (8) Dilated gall-bladder,
- (9) Multiple puncture wounds,
- (10) Slight cystitis.

COMMENTS

The most striking points in the case are:

1. The association of silicosis of the lung with amyloidosis of the kidneys and the spleen.

2. The absence of any chronic infection of pulmonary structures accompanying the silicosis; and the absence of any other focus of chronic suppuration or of infection to explain the amyloidosis. The pyelitis clinically was of a transient character and no evidence of its presence was found post mortem.

3. The uremic death was due apparently to amyloidosis. In this connection it was thought clinically that the pye-

litis might account for the kidney insufficiency (nephritis), but since the pyelitis cleared up and no evidence of it was found post mortem, it is probable that the renal insufficiency was on an amyloid basis originally and that the pyelitis was a secondary and transient factor only. Nephritis with renal insufficiency of glomerular type resulting from a pyelitis is in itself a rarity and is only occasionally found in a few cases of very persistent low grade chronic pyelitis.

The question which naturally arises is whether the silicosis (pulmonary) was responsible for the amyloid change in the kidneys and spleen. No record of such an association could be found in the literature. Amyloidosis has been produced experimentally in mice and rabbits by injection of sodium silicate solutions, but inasmuch as amyloidosis can be produced in these animals by almost any chemical or infectious material such results cannot well be applied to man.^{1,2,3}

The possibility that the amyloid change was initiated by trauma must be considered. There is little evidence to be derived from the literature on this matter. Some German reports indicate that an attempt has been made in that country to connect nephritis with trauma, but since German compensation medicine is so highly organized such an opinion is hard to evaluate. No reports of any such connection are found in the American, English or French literature. More pertinent to our case is the report of von Schnitzer,⁴ but such evidence as he presents seems quite insufficient to prove a relationship between trauma

and the production of amyloid. Perhaps more cases presenting the association of silicosis and amyloidosis or trauma and kidney lesions may be reported in the future, therewith

bringing enlightenment; but until more such data is collected it seems best to report simply an association or coincidence rather than a probably explicable relationship.

REFERENCES

- ¹YOKOI, Y.: Amyloid formation due to injection of blood and sodium silicate solution in mice, *Trans. Jap. Path. Soc.*, 1928, xviii, 237.
- ²SATO, S.: Influence of extirpation of one kidney upon amyloid formation due to intravenous injection of sodium silicate solution in rabbit, *Trans. Jap. Path. Soc.*, 1928, xviii, 240.
- ³MURATA, M., and YOSHIKAWA, S.: Experimentelle Erzeugung von Amyloidose durch orale und parenterale Verabreichung der Kieselsäure und einer ihrer Verbindungen, *Virchow's Arch. f. path. Anat.*, 1927, cclxiv, 587-604.
- ⁴VON SCHNIZER: Angeblicher Zusammenhang zwischen Amyloidniere und Dienstbeschädigung abgewiesen, *Med. Klin.*, 1926, xxii, 776-777.
- ⁵NOBLE, J. F., and MAJOR, S. G.: Renal insufficiency in amyloid disease, *Arch. Path.*, 1929, viii, 762-774.

At a meeting of the Board of Regents of the American College of Physicians at San Francisco, California, April 8, 1932, the following appreciation was ordered spread upon the Minutes:

An Appreciation

DR. CARL VERNON WELLER

ANN ARBOR, MICHIGAN

BY THE

BOARD OF REGENTS

OF THE

AMERICAN COLLEGE OF PHYSICIANS

"The Board of Regents of the American College of Physicians desires at this time to record its highest appreciation of the valuable services of Dr. Carl Vernon Weller, as Editor of the ANNALS OF INTERNAL MEDICINE during the years 1931 and 1932.

"Accepting the mantle of his great chief, Dr. Aldred Scott Warthin, he carried on in the same spirit of enthusiasm and devotion to scientific ideals that had brought the Annals to its high place in the field of medical journalism.

"It is a further privilege to accord to Dr. Weller the fullest recognition for giving so freely of his scholarly talents. By his constant endeavor to maintain the high standards of the Annals, he has extended the influence of the College and has contributed in no small measure to the advancement of Internal Medicine in America."

WALTER L. BIERRING

JOHN H. MUSSEY

DAVID PRESWICK BARR

Committee

Editorial

The Editorship of the ANNALS OF INTERNAL MEDICINE is accepted as a trust from the College and from the former Editors. Into the building of this journal have gone the thought, the faithful work, something of the ideals, and indeed a part of the lives of those who have previously held this position. The service which the Annals now renders the College and the medical profession and its standing among medical publications are the results of their labors. Tribute is due especially to Aldred Scott Warthin, who took over the task at a stage when to obtain contributors to ensure a monthly appearance was still a struggle, and who for seven years, by personal effort, by stimulating contributors and often assisting them, by judgment in selection, by endless patient care with the copy and the proof, brought the Annals through the difficulties of this formative period to the established position it now holds. When death suddenly cut short his achievements in this and many other fields, his colleague and successor in the Chair of Pathology at the University of Michigan, Dr. Carl Vernon Weller, in answer to the appeal of the College, became also his successor in the Editorship of this journal. It has grown stronger in his capable hands. The group of contributors has become constantly larger and the quality of the papers selected for publication has steadily risen. The increasing circula-

tion of the Annals at home and abroad is the best evidence of the importance of its contents. In appearance and in uniformity of typographical style, great gains have been made through Dr. Weller's conscientious and time-consuming labors in the technical aspects of the editor's task. The results of all these accomplishments are now placed in the hands of the new Editor. It is for him to attempt to guide this publication so that it may show still further progress along the path first broken and then marked out by his predecessors. What success his untried capacities may enable him to achieve he feels will be due largely to the example that has been set him of devotion to the task.

Among the functions of the Annals is that of publishing the most noteworthy of the addresses and of the clinics delivered at the annual meeting of the College. In this respect it takes the place held by the "transactions" of other societies. These articles in the Annals will serve more and more as a yearly summary of the important advances in the field of internal medicine and its allied sciences. To the Fellow who has been unable to attend the meeting, the Annals brings some compensation in the form of the published articles; to him who has been aroused and stimulated by the speakers at the Sessions, there is even greater value in having the addresses in permanent form.

In addition to the material derived from the annual meeting, the *Annals* contains each month a number of articles which have been submitted directly to the Editor. There are at present several times as many manuscripts submitted as can be printed in a journal of the *Annals'* size. The Editor is therefore forced to adopt certain principles of selection. Naturally the first selection will be based on quality. The completeness of data, the reliability of methods, the consideration given to the work of others, the proof offered in support of assertions should all be weighed before a manuscript is accepted. Papers may be free from defects of quality, however, and yet fail in competition with others when judged as to relative importance. The Editor realizes his inability to predict the possible future importance of all facts: his standard will have to be the present interest and significance of the data offered. The formal and elaborately documented study of minor or trivial phenomena should find no place in the pages of the *ANNALS OF INTERNAL MEDICINE*.

The results of thorough investigations of real significance may sometimes have to be rejected by the Editor in favor of a paper of equal merit but on a subject more directly within the scope of internal medicine. This field certainly should not be defined too nar-

rowly: it blends indeed without sharp boundary into all the medical sciences and all the clinical specialties. Nothing in science or practice is truly foreign to its interests. The Editor, however, is of those who believe that the essence of internal medicine consists of careful clinical observation of disease and its response to treatment.

It is hoped that many of the articles eventually selected will have been written by members of the College, so that the *Annals* may serve the members of the College both in bringing advances in medicine to their notice and by facilitating the publication of their own work.

The editorial sheet of the journal offers to the reader brief analyses of interesting topics in the field of medical science or practice. The Editor will frequently solicit editorials from authorities in special fields. It is a further function of the editorial sheet to serve as a voice for the College. It will be open to receive such statements as from time to time our Officers, Boards of Regents and Governors, or the Committee on Public Relations may wish to make. Such comment as the Editor may utter upon educational, economic, or ethical problems of internal medicine will have no official character and for such views he in advance accepts personal responsibility.

Reviews

Hypnotism—Suggestion and Faith-Healing.

By ALEXANDER CANNON, M.D. William Heinemann Ltd., London, 1932. 43 pages. Price, 2s 6d net.

It is difficult to believe that this book is addressed to physicians, because lay people with a reasonable degree of critical judgment would refute the over-simplification and extravagant claims made by the author. Hypnotism, to the author, is a cure-all for many disorders and his faith in it is unbounding. The only value to the book is the brief presentation of others' methods of hypnotic technic. The discussion of suggestion is limited and highly colored by the author's dubious notions, and there is nothing informative about faith-healing. None of the dangers of hypnotism are mentioned and there are many. In the history of Medicine the story of the use of hypnotism and suggestion has been colored with an atmosphere of charlatanism. It is especially unfortunate, under these circumstances, that in this book a more critical attitude should not have been maintained. Most psychotherapists would probably admit that hypnosis is a helpful adjunct in their work but that its use is limited to certain well selected material and for special purposes. Actually, it is difficult to see a reason for the publication of this particular book.

R. P. T.

The Child and the Tuberculosis Problem.

By J. ARTHUR MYERS, Ph.D., M.D., F.A.C.P., with an introduction by WILLIAM P. SHEPARD, M.D., F.A.P.H.A. xvi + 230 pages, with 21 illustrations. Charles C. Thomas, Springfield, Illinois. 1932. Price, \$3.00.

With his experience as head of the Lymanhurst School for Tuberculous Children, the author has been exceptionally able to produce a book that general practitioners, pediatricians, school physicians, health officers, public health nurses, social workers, school

administrators, and executives of local tuberculosis associations, especially, should find of value. This monograph contains a clear and concise discussion of diagnostic measures, particularly those most valuable in diagnosing tuberculosis in children, viz., tuberculin skin tests and roentgen examination. In it also are the newer ideas concerning the etiology, pathogenesis, and diagnosis of the disease. The chapters on the finding of tuberculous children and the disposal of cases examined for the disease are well treated and should be studied by those interested in childhood tuberculosis. One of the most worthwhile parts of the book is that dealing with concrete suggestions for organizing a plan of work for the prevention of tuberculosis in the future. Emphasis is placed on the control of the disease among domestic animals and the contributions of veterinarians commended. Attention is called to the need of controlling tuberculosis among members of families and of outlining a method for the reduction in its occurrence among nurses. Each chapter is followed by a helpful summary; at the end of the book there is a bibliography of well chosen and recently published material.

A. H. F.

Diagnosis and Treatment of Diseases of the Thyroid Gland.

By GEORGE CRILE and Associates, 508 pages with 164 illustrations. W. B. Saunders Company, Philadelphia, 1932. Price, \$6.50 net.

This book cannot fail to be of great interest to all those concerned with the clinical aspects of the goiter problem. It presents very clearly the experience and point of view of one of the largest and most successful thyroid clinics. A large part of the book is devoted to chapters on special topics such as those on the cardiac symptoms, the ocular changes, the cutaneous manifestations, the laryngeal disturbances, the

alterations in carbohydrate metabolism, the relationship to joint lesions and to infections, and the association with syphilis and tuberculosis. These topical discussions are of great interest to the internist. Preoperative and postoperative management are well presented and there is an interesting account of postoperative complications.

The chapters on more general subjects, such as those on diagnosis of hyperthyroidism and on hypothyroidism, are clearly written but rather elementary in character and often omit mention of interesting work in other clinics. The surgical chapters are of interest even to the medical man. The bold treatment of postoperative lung complications by tracheotomy and suction is thought-provoking. A more detailed analysis of the results obtained would be helpful.

This book is by no means a complete consideration of goiter, but it is a very readable account of present day practical aspects of the goiter problem.

M. C. P.

The Differential Diagnosis of Endocrine Disorders. By ALLAN WINTER ROWE. 220 pages. The Williams & Wilkins Company, Baltimore, 1932. Price \$4.00.

The author of the book is the President of the Association for the Study of Internal Secretions, and Director of Research, Evans Memorial, Massachusetts Memorial Hospitals, in Boston. The prominence of the writer gives the contents of the book an authoritative stamp.

The material presented is based upon an elaborate study of over 5000 cases during the past twenty years. The author believes that a diagnosis should be based upon a thorough routine study supplemented at times by further special examinations, and the reader will get the impression that the "material represents the accurate, sincere, interested labor of a large group of highly trained individuals." Emphasis is placed upon the importance of differentiating between endocrinopathies and conditions simulating them but due to an underlying etiology not associated with the ductless glands. With this in mind the author has inserted in the text a table correlating with a large series of cases and the endocrine glands in some of the more common diseases. This is a

The contents are divided into three sections: SECTION I, Clinical Considerations; SECTION II, Laboratory Measurements; SECTION III, Special Examinations. They are based entirely on the work of the one clinic, the rarer endocrinopathies are not considered, and reference to animal experimentation is purposely omitted. In the beginning the cases are divided into five groups: pituitary, thyroid, gonad, adrenal, and pancreas, without reference to phases of over- or underactivity, and analyzed according to symptoms, physical signs, and laboratory tests. The last two groups (adrenal and pancreas) contain only fifteen cases each and many of the data connected with them were considered not significant. They were nevertheless included in the tables.

The title of the book is somewhat misleading. The cases have already been diagnosed and pigeonholed in the different groups which are now subjected to minute analysis. The author mentions the necessity of the proper integration of a diagnostic study but of this important factor in diagnosis the monograph contains hardly a trace. Chapter XIV on "Differential Diagnostic Illustrations", consisting of less than four pages, might well have been considerably amplified.

The work should be welcomed by those especially interested in this field by reason of the valuable data it contains, but the busy physician may be disappointed if he expects a clear and concise aid in the differential diagnosis of endocrine disorders. The material is there but he must dig it out for himself. The index will be of some aid in the task.

Statistics, like those in Section I especially, do not constitute a pleasant diet for the practitioner and an unusual diction, combined with a somewhat involved style, will not whet his appetite. The contents of Section II flow more freely and more successfully hold the reader's interest.

T. P. S.

Outline of Preventive Medicine for Medical Practitioners and Students. Prepared under the auspices of the Committee on Public Health Relations, New York Academy of Medicine. 24 contributors. 2nd Ed.

tion revised and enlarged. Paul H. Hoeber, Inc., New York, 1932. Price, \$5.00. The second and enlarged edition of this book testifies to its usefulness. It is an outline of preventive medicine summarizing those opportunities which present themselves in daily practice for the institution of preventive measures. An orienting chapter on the incidence of disease presents briefly and clearly the nature of the problem of prevention of specific diseases or complications of diseases in the fields of general medicine, surgery, obstetrics, pediatrics, and other specialties is dealt with in separate chapters. Venereal diseases and tuberculosis

are discussed as special topics. There is a rather brief chapter on occupational diseases. The field is such a large one that in the brief space allotted to each topic it is sometimes not possible to furnish more than general therapeutic principles instead of the specific instructions which the practitioner might desire. For the most part, however, the recommendations are definite and practical. The general tone of the book is conservative; it deals with the preventive measures which are feasible today. It will stimulate any physician to realize how much he may accomplish in this field and how real and undivided is his responsibility.

M. C. P.

College News Notes

Announcement is made of the following gifts to the College Library of publications by members:

- Dr. C. F. Morsman (Fellow), Hot Springs, S. D.—6 reprints;
- Dr. Henry M. Moses (Fellow), Brooklyn, N. Y.—3 reprints;
- Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—1 reprint;
- Dr. George W. Parker (Fellow), Peoria, Ill.—1 reprint;
- Dr. Audley O. Sanders (Fellow), Palo Alto, Calif.—2 reprints;
- Dr. John F. Kenney (Associate), Pawtucket, R. I.—2 reprints;
- Dr. Curran Pope (Associate), Louisville, Ky.—1 reprint.

Dr. V. C. Rowland (Fellow), Cleveland, addressed the State Conference of Ohio Health Commissioners at Columbus, November 17, on "Preventive Medicine and Periodic Health Examinations."

Dr. E. J. G. Beardsley (Fellow), Philadelphia, was a guest of the Guthrie Clinic of Sayre, Pa., on November 2, 1932. He was the guest speaker at a joint meeting of the Bradford and Tioga County Medical Societies at Troy, Pa., that evening, his

subject being "The Cardiovascular Disorders of Everyday Medicine."

Dr. Stewart DeWitt Conklin (Fellow), Sayre, Pa., is Associate in Medicine at the Robert Packer Clinic and Hospital and Secretary of the Bradford County Medical Society.

Dr. Charles H. DeWan (Fellow) and Dr. Ronald L. Hamilton (Fellow) are the Pathologist and Cardiologist, respectively, at the Robert Packer Clinic and Hospital.

Dr. Edwin Henes, Jr. (Fellow), Milwaukee, retired as the Executive Secretary of the Inter-State Postgraduate Medical Association of North America following their October Meeting at Indianapolis. Dr. Henes had completed a decade of service to the Association, during which time he assisted in the arrangement for, and presentation of, ten International Assemblies. Dr. Henes retired due to the condition of his health. He will spend several months abroad.

Dr. Albert H. Rowe (Fellow), Oakland, Calif., delivered a paper entitled, "The Present Status of Food Allergy as Related to Bronchial Asthma," before the Kings

County Medical Society at Seattle, Wash., on October 24.

Dr. Albert S. Hyman (Fellow), New York City, Director of the Witkin Foundation for the Study and Prevention of Heart Disease, addressed the Yorkville Medical Society November 21, 1932, upon "Recent Advances in the Study and Treatment of Angina Pectoris."

On November 16, 1932, Dr. Hyman addressed the New York Physicians Association on "Heart Pain."

Dr. Howard T. Phillips (Fellow), Wheeling, W. Va., read a paper before the Raleigh County (West Virginia) Medical Society December 1, 1932, on "Diagnosis and Treatment of Some Common Skin Diseases."

At the November 21, 1932, Meeting of The Medical Association of the Greater City of New York, the following Fellows participated as indicated:

Dr. Edward E. Cornwall, "The Treatment of Pneumonia by Physiological Support."

Dr. LeGrand Kerr, "Pneumonia in Children."

Dr. Henry M. Moses, discussion of the above papers.

Dr. Samuel A. Brown (Fellow) is now Dean Emeritus of New York University Medical College. Dr. Warren Coleman (Fellow) has been appointed Professor of Clinical Medicine at this institution.

Dr. Howard T. Karsner (Fellow), Professor of Pathology at Western Reserve University School of Medicine, Cleveland, has been elected the member for the United States of the Comité Directeur of the International Society for Geographic Pathology.

Dr. Harold Swanberg (Fellow), Quincy, Ill., editor of the Jackson County Medical Society, Jackson, Tenn., December 6, on "Ruben Therapy in General Practice."

Dr. Arthur C. Morgan (Fellow), Philadelphia, was a member of the Committee

on the Costs of Medical Care during its five-year study. Dr. Morgan has recently given talks on "Public Health Consciousness" in Philipsburg, Erie, Clearfield, St. Mary's and Conshohocken, Pa.

Dr. Henry O. Colomb (Associate) has recently assumed the position of Clinical Director of the Springfield State Hospital, Sykesville, Md.

Dr. Louis Faugeres Bishop, Jr. (Fellow), New York City, was elected to Fellowship in the New York Academy of Medicine at a stated meeting, November 3, 1932.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., recently addressed the Monmouth County (New Jersey) Medical Society at the Monmouth Memorial Hospital, Long Branch, on "Recent Advances in the Treatment of Anemias" and discussed "A New Antispasmodic Remedy—'Perparin'."

The following are recent additions to the valued list of advertisers in the ANNALS OF INTERNAL MEDICINE:

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Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. Bernard L. Wyatt (Fellow), Tucson, Arizona—1 book, "Chronic Arthritis and Fibrositis";

Dr. J. G. Archer (Fellow), Greenville, Miss.—1 reprint;

Dr. H. L. Arnold (Fellow), Honolulu, Hawaii—1 reprint;

Dr. Roy W. Benton (Fellow), Milwaukee, Wis.—1 reprint;

Dr. I. D. Bronfin (Fellow), Denver, Colo.—1 reprint;

Dr. William R. Brooksher, Jr. (Fellow), Fort Smith, Ark.—2 reprints;

Dr. Grafton Tyler Brown (Fellow), Washington, D. C.—1 reprint;

Dr. Harold N. Davidson (Fellow), Atlantic City, N. J.—4 reprints;

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—2 reprints;
 Major C. C. Hillman (Fellow), Manila, P. I.—1 reprint;
 Dr. John F. Kenney (Associate), Pawtucket, R. I.—1 reprint;
 Dr. Allen K. Krause (Fellow), Tucson, Arizona—2 reprints;
 Dr. W. Paul Holbrook (Fellow), Tucson, Arizona—2 reprints;
 Dr. Max Pinner (Fellow), Tucson, Arizona—4 reprints;
 Dr. Roy D. Metz (Associate), Detroit, Mich.—1 reprint;
 Dr. B. S. Pollak (Fellow), Secaucus, N. J.—1 reprint;
 Dr. Wm. C. Pollock (Fellow), Denver, Colo.—1 reprint;
 Dr. Willard H. Squires (Associate), New York City, N. Y.—1 reprint;
 Dr. M. J. Synnott (Fellow), Montclair, N. J.—1 reprint.

The Southern California Members of the American College of Physicians gave a dinner in honor of Dr. F. M. Pottenger, then President of the College, at the California Club, Los Angeles, January 12. Dr. David P. Barr (Regent), Professor of Medicine at Washington University, St. Louis, the guest speaker, delivered the address of the evening.

Dr. James S. McLester (Fellow) and Dr. Charles M. Nice (Fellow) were recently elected Physicians-in-chief to Section A and Section B of the Medical Staff of the Hillman Hospital, Birmingham, Alabama. At the same time, they were appointed Chairman and Secretary, respectively, of the Advisory Board of the Hospital.

Dr. George R. Minot (Fellow), and Dr. Chester S. Keefer (Fellow), both of Boston, Mass., addressed the Boston Orthopedic Club at their symposium on arthritis.

Dr. Minot in November addressed the Toronto Academy of Medicine on the Treatment of Anemia. He was also one of the speakers at the celebration held at the Harvard Medical School December 20, 1932 to commemorate the 150th anniversary of the founding of the "Professorship of the Theory and Practice of Physic" at Harvard.

Dr. Albert F. R. Andresen (Fellow), Brooklyn, New York, addressed a meeting of the Atlantic County Medical Society, Atlantic City, N. J., November 18, 1932, on "Gastrointestinal Manifestations of Food Allergy". He lectured again on the same subject at one of a series of Friday Afternoon Practical Lectures, at the Jersey City Medical Center on January 13, 1933.

On January 6, Dr. Andresen gave a lecture on "The Diagnosis and Treatment of Biliary Tract Diseases" before the Cortland County Medical Society, Cortland, N. Y., one of a series of postgraduate lectures to county medical societies fostered by the Medical Society of the State of New York.

Dr. Max Einhorn (Fellow), New York City, N. Y., addressed a clinical conference of the Madison Park Hospital, Brooklyn, New York, January 13 on "Indications for Operations in Gall-Bladder Diseases", which was discussed by Dr. Albert F. R. Andresen (Fellow), of Brooklyn.

At the recent meeting of the American Association for the Advancement of Science at Atlantic City, N. J., Dr. Walter M. Simpson (Fellow), Dayton, Ohio, was elected Secretary of Section N (Medical Sciences) for a period of three years.

Dr. Edward J. Engberg (Fellow), St. Paul, Minn., was the guest speaker at a joint meeting of the Eastern Montana Medical Society and the Southwestern District Medical Society of North Dakota at Dickinson during the past autumn. His subject was "Treatment of Psychiatric Patients in Private Practice".

Dr. W. H. Kraemer (Fellow), Wilmington, Delaware, delivered an address on "A Discussion on the Clinical Application of Lead Therapy as a Research Feature of the Tumor Clinic" before the Post Graduate Clinic at the Lankenau Hospital, Philadelphia.

Major Edgar Erskine Hume (Fellow), formerly attached to the Adjutant General's Office, Boston, Mass., was transferred to Washington, D. C., at the end of September,

1932, when he became Librarian of the Army Medical Library.

Major C. C. Hillman (Fellow), since November, has been on duty at the Sternberg General Hospital, Manila, P. I.

Dr. P. P. McCain (Fellow), Sanatorium, N. C., recently read a paper on "Childhood Tuberculosis" before the Seaboard Medical Association at Rocky Mount, N. C. He also delivered a public address on the subject "Prevention of Tuberculosis" with the child as the important point of contact.

Dr. McCain addressed the State Radiological Society at Asheville recently on the subject of "Radiograms in the Diagnosis of Childhood Tuberculosis", and he has been selected as the guest speaker at the meeting of the South Carolina Medical Association at Greenville.

A testimonial dinner was recently tendered Dr. J. P. Munroe (Fellow), Charlotte, N. C., at the Charlotte Country Club. Addresses in appreciation of Dr. Munroe's work both within and without the State, but particularly in Charlotte, were made by several members of the local County Medical Society. Addresses were also delivered by Dr. J. T. Burrus, President of the State Board of Health and by Dr. L. B. McBrayer (Fellow), Secretary-Treasurer of the Medical Society of the State of North Carolina.

Dr. W. B. Kinlaw (Fellow), Rocky Mount, N. C., was elected Secretary of the Seaboard Medical Association at its recent meeting.

On January 1, Dr. Henry S. Houghton (Fellow), formerly Dean of the University of Iowa College of Medicine, assumed his duties as Associate Dean of the Division of Biological Sciences, University of Chicago, and as Director of the University Clinics. Dr. Houghton served as Dean of the Harvard Medical School of China, located at Shanghai from 1911 to 1917, and as Acting Director and Director of the Peking Union Medical College from 1916 until 1924, where-

upon he became Dean of the University of Iowa College of Medicine.

Dr. Peter T. Bohan (Fellow), Kansas City, Mo., was recently elected President of the Kansas City Southwest Clinical Society.

Dr. Benjamin W. Black (Fellow), Oakland, California, and Dr. Joseph C. Doane (Fellow), Philadelphia, are members of the Council on Community Relations and Administrative Practice recently appointed by the American Hospital Association to make an immediate study of the recommendations of the Committee on the Costs of Medical Care.

Dr. Augustus W. Crane (Fellow), Kalamazoo, Mich., was elected President of the Michigan Association of Radiologists recently organized.

Dr. C. Brewster Brainard (Fellow), Hartford, Conn., was recently elected President of the Hartford Medical Society. Dr. Robert S. Starr (Associate), was elected Vice-President.

Dr. Charles W. Burr (Fellow), Philadelphia, Pa., recently presented 19,000 books to the University of Pennsylvania Library. In 1928 Dr. Burr presented this library with a valuable collection of autographs and has on previous occasions donated about 700 other volumes.

Dr. Francis H. Smith (Fellow), Abingdon, Va., was recently elected one of the Vice-Presidents of the Medical Society of Virginia.

Dr. J. Gurney Taylor (Fellow), Milwaukee, Wis., is President of the Wisconsin Anti-Tuberculosis Association.

Dr. William S. Middleton (Fellow), Madison, Wis., was elected Vice-President of the Central Society for Clinical Research at its recent annual meeting in Chicago. Dr. William H. Bunn (Fellow), Youngstown, Ohio, was reflected Treasurer.

OBITUARY

DR. WILLIAM ENGELBACH died November 22, in St. John's Hospital, Springfield, Illinois, of heart disease after an illness of three months. As a Fellow of the College since January 14, 1920, he always took an active interest in its affairs.

Dr. Engelbach was born in Arenzville, Illinois, in 1877. He obtained the degrees of Bachelor and Master of Science from Illinois College in 1899. Northwestern University Medical School awarded him the degree of Doctor of Medicine in 1902, following which he spent several years in post-graduate study in Berlin, Paris, and Vienna. Returning to the United States he decided to affiliate with the St. Louis University School of Medicine where he served as an Instructor in Medicine from 1909-1911, and Professor of Medicine from 1911-1924.

His Hospital connections were as varied as his interests in Internal Medicine. He served as Chief of Staff of St. John's Hospital (St. Louis) from 1909-1924, and was a member of the Staffs of the City Hospital, Missouri Baptist Sanatorium, Maternity Hospital, and New Jewish Hospital for many years. During the War, service to his country was rendered as Chief Physician of Examining Board No. 1 in St. Louis.

Dr. Engelbach's interest was always with organized medicine in its broadest sense. His executive ability was an outstanding quality and his services were ever in demand when matters concerning the general profession were discussed. He was characterized by an untiring energy in the affairs of medicine. This was evidenced as a

member of the local and state medical societies in Missouri and as President of the St. Louis Medical Society in 1918. After removing to New York in 1931, where he opened an office at 897 Park Avenue for the practice of Internal Medicine, he became a member of the New York State Medical Association. He was a Fellow of the American Medical Association and a member and ex-President (1922-1923) of the Association for the study of Internal Secretions.

As a clinician in the truest sense of the word he contributed greatly to medical literature by his many writings. He was the author of numerous articles published in various medical journals and was a contributor to Tice's *Practice of Medicine*. While his interest lay in all fields related to Internal Medicine perhaps his greatest interest was in the disorders of the ductless glands. Bringing to the subject a broad general knowledge of medicine, the keenness of observation of the seasoned clinician, the breadth of view that is not restricted by prejudice and preconception, he was able to clarify the subject and reduce chaos to something simulating order. His clinical observations served as a basis for classification of the various phases of a most difficult subject. He was unquestionably one of the foremost clinical investigators in the field and time alone will determine the ultimate value of his contributions.

To achieve what was considered the most important work of his life, the summation and publication of his knowledge obtained from years of ob-

servation of the endocrine dyscrasias, he retired from active practice in 1929 and devoted nearly two years to the preparation of a three volume series entitled "Endocrine Medicine." The resumption of his practice in 1931 in New York was curtailed by his final illness.

Medicine has lost in the demise of Dr. Engelbach one of its most stalwart sons. Eager, enthusiastic, earnest, kindly and considerate, a scholar, scientist, teacher and gentleman, he

gave to the practice of medicine his entire personality, his interests, and an untiring devotion and sympathy. He received from his practice a knowledge of work well done, of effort rewarded by the appreciation on the part of all patients, students, associates and colleagues who were fortunate enough to come under his influence.

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The Senile Patient*

By LEWELLYS F. BARKER, M.D., F.A.C.P., *Baltimore, Maryland*

SOME of you may be wondering how anyone connected with the Johns Hopkins Hospital dare say anything in public about the later life of man in view of the commotion aroused by our great internist, the late Dr. Osler, some years ago through his semi-serious, semi-jocular remarks upon the ages of forty and sixty; but the chairman of our Program Committee, Dr. George W. Crile, whose word is law, has assigned to me as a topic "The Senile Patient", and I must take the risk!

PHYSIOLOGICAL AND PATHOLOGICAL SENILITY

With your permission, I shall interpret the term "senile patient" as meaning simply "a patient advanced in years", avoiding by this definition any necessary connotation of preternatural mental or physical infirmity due directly to old age. For there is, you will grant, an old age that is, relatively speaking, "physiological" as well as a "pathological" old age.

Though a unicellular organism may live on indefinitely, every multicellular

organism grows old and ultimately dies. Though its constituent cells may, in cultures in vitro, seem to be potentially immortal, the aggregate of cells of a metazoan animal is definitely mortal. Old age and death are the price paid for the differentiation and specialization of function, characteristic of organisms made up of many cells and tissues that are reciprocally interdependent.

Though there are great differences in the length of life of the individual members of the human species, and though the average duration of human life has been steadily increasing for centuries and more rapidly during recent years (from thirty-five in 1880 to fifty-five in 1920), it is the expectation of life of children at birth and of people in the earlier decades of life that has been most markedly increased; the gain in the expectation of life of persons fifty years old has been only 1.35 in eighty years, whereas the expectation of life for older groups has been growing less, owing to the prolongation of the lives of weaker persons by means of our modern methods of curative and preventive medicine. Many human beings still reach

*Address to the Interstate Postgraduate Assembly, Indianapolis, Ind., Oct. 25, 1932.

the age of ninety or one hundred, but there is, as yet at least, but little if any scientific evidence that the maximal span of human life can be materially increased by any measures that are likely to be devised for the improvement either of man's environment or his heredity. It may not be possible to extend average longevity beyond the age of sixty—almost certainly not if the euthenic practices of the present are not to be supplemented by eugenic practices, to which many are antipathetic.

Biostatistical studies have thrown much light upon the factors that determine the span of life for the human individual. Though longevity depends partly upon inherited constitution, partly upon environment, the evidence strongly favors the view that, on the whole, factors of inheritance are of greater importance than environmental factors. Many years ago, in one fairly large aggregate of persons studied (the Hyde family), it was found that a group that had both fathers and mothers who lived to eighty or more years had an average duration of life of 52.7 years, whereas in the same aggregate, another group in which both parents died before sixty had an average duration of life of only 32.8 years, a difference of practically twenty years. From this and other evidence available the well-known aphorism "To live long, select long-lived parents" would seem to be justified!

In "physiological" old age, there is a gradual process of cell atrophy and a relative increase in the interstitial tissues at the expense of the parenchyma of the organ-system—an involution of the organism as a whole comparable in process to the involution

of single parts of the organism (such as the branchial clefts, the placenta, and the ovaries) occurring at different stages of life. The late Dr. A. S. Warthin spoke of this aging of the whole organism as "the major involution" and of the aging of single parts as "minor involutions"; and he thought that involution was as important as evolution in the great procession of life, minor involutions occurring when parts are no longer of use to the organism, the major involution taking place after the organism as a whole has passed through the periods in which ordinarily the fundamental biological functions have been fulfilled. Theoretically, then, senescence is as physiological as growth; both are inherent in the quality of the germ-plasm inherited. With the best germ-plasms and favorable environments the duration of life of higher organisms is rarely greater than five times the number of years of development to maturity and if the latter for man be taken to be twenty-one, the maximal span of human life cannot much exceed one hundred years, though through preventive medicine and hygiene we may increase average longevity a little more and may swell the numbers of human beings that enjoy a "physiological" old age. But it is better for the race that human individuals live not too long. Thoughtful men must agree with Goethe's statement, "Death is Nature's device for securing abundant life".

THE CAUSES OF DEATH AMONG THE OLD

The very old die from causes very different from those that are responsible for the death of younger persons.

By virtue of their inborn qualities of resistance, their good nutritive and reparative powers, the harmonious activity of their several organ-systems, their habits, and their good fortune in the avoidance of lethal exogenous influences (traumata; infections), they have reached advanced years of life, but they ultimately die either from the break-down of some important organ system or from trauma or suicide. The recent statistical studies of Pearl and Raenkham show that with advancing adult age there is a steady decrease of the percentage of total mortality due to diseases of organ-systems normally directly exposed to and in contact with the external environment, whereas there is an increase of the percentage of total mortality due to diseases of organ-systems not exposed to direct contact with the external environment.

Nearly half of our old people die from diseases of the circulatory system (cardiac failure; arterial disease; cerebral hemorrhage); about one-eighth from diseases of the respiratory system (especially lobar and bronchopneumonia); about one-eighth from cancer; about one-twelfth from renal disease; about one-fifteenth from diseases of the digestive system; and the rest from diseases of other organ systems, traumata, or ill-defined diseases reported as "deaths from senility". The last mentioned cause of death should rarely, if ever, be reported; if a definite cause has not been made out, it is wiser to report "death from unknown cause". The majority of deaths among old people occur during the winter months of the year; and more die during the latter half of the night than during the day and the first half

of the night. If you have not read the excellent paper by Dr. Alfred Worcester entitled, "The Care of the Dying", let me urge you to do so.

THE SOMATIC AND PSYCHIC INFIRMITIES OF LATER LIFE

All normal people desire long life, but they usually add the proviso that they shall continue to enjoy both bodily and mental health. As Talleyrand wittily said years ago, "Everybody wants to live long; but nobody wants to be old." Very few people in early life would willingly look forward to a long period of senile decrepitude or chronic invalidism. In his description of the Struldbugs (who lived forever), Swift painted their plight as so pitiable, when they were observed by Gulliver at Laputa, that any form of death seemed preferable to the continuance of such a life.

The physical infirmities of old age have been much studied through the centuries; since the earlier descriptions of non-medical writers in the Ninetieth Psalm, in Ecclesiastes, and in the literature of the Greeks and the Romans, medical men at all times have been interested in the gradual physical deterioration of the structures and functions of the human body in those who live long. Beginning with failure of accommodation in the eyes, change in the color and abundance of the hair, gradual loss of the teeth, diminution of sex potency, and increased fatigability, a whole series of other changes are prone sooner or later to become evident, until, if life continue long enough, the fully developed picture of senility is presented. The height is slightly reduced, a stooping posture is assumed, the body-weight decreases,

the bony prominences become more marked, the joints stiff and the muscles flabby, the skin is wrinkled, and shows hyperkeratoses, the arcus senilis appears, the breasts and the abdominal wall become pendent, the thorax grows rigid with shallow respiration and tendency to bronchitis, the arteries thicken, become tortuous, and sometimes calcified, varicose veins and hemorrhoids are common, digestion is slowed with diminution of hydrochloric acid in the gastric secretion and tendency to flatulence and constipation. In men there is difficulty in starting the flow of urine and of complete emptying of the bladder owing to hypertrophy of the prostate, atony of the bladder or both; the genitalia atrophy, the endocrine glands become less active (as shown by the lowered basal metabolic rate, the sensitiveness to cold, the tendency to hyperglycemia and glycosuria, and the changes in libido and potentia), and the sensory functions, motility, and coördination become more or less impaired.

Of the psychic manifestations of later life, some are referable to cognitive, some to affective-conative domains. Among the earlier symptoms are forgetfulness of names, a diminution of the instinctive urges (sex, food, social life), and lack of receptivity of new ideas. Later on, there may be loss of memory for recent events, difficulties of attention, concentration and orientation, somnolence in the daytime and insomnia at night. If the cerebral arteries undergo marked changes, pseudobulbar and other paralyzes (with or without aphasia and apraxia) may result, or changes in the psyche (e.g. sensitivity, lack of re-

gard for the welfare of others, stubbornness, tendency to suspicion, fall of the ethical level, pathological irritability and emotionalism) may follow. Whether outspoken "senile dementia" (with confusion, illusions, and delusions) and "second childhood" are to be regarded as merely the expression of an intensification and rapid progress of physiological involution of the cerebral cortex, or are to be kept separate from the latter as something more specific, are matters still under discussion. The relations of senile dementia to cerebral atherosclerosis, to Alzheimer's disease, to Pick's disease, and to other organic and functional psychoses of the senium and presenium can scarcely be dealt with in a brief paper such as this, though there is a large and growing bibliography of the subject.

GENERAL COMMENTS UPON DISEASES IN PERSONS ADVANCED IN YEARS

Students of geriatrics or presbyiatrics (the branch of medicine that deals with diseases of the old) have distinguished between the maladies that are largely restricted to the aged and the diseases that occur in both the young and the old.

Among the former are Paget's deforming osteitis, senile osteoporosis and *malum coxae senile*, senile anorexia, diverticula of the esophagus and intestine, coproliths, senile bronchial catarrh, senile emphysema, prostatic hypertrophy and its sequelae, cerebral atherosclerosis, senile dementia, paralysis agitans (non-encephalitic in origin), and hyperkeratosis. Carcinoma, too, is much more frequent in the second than in the first half of

life, though in extreme old age its incidence lessens.

Among the diseases that occur in both the young and the old, those of the circulatory and of the respiratory system predominate in the old, but the symptomatology may vary considerably from that observable in the young. In vigorous old people, it is true, the clinical phenomena may not be very different, but in older people in whom characteristic involutional changes have already occurred, we meet with many bizarre, atypical, and more or less confusing clinical pictures.

It has been especially emphasized by internists of experience that *acute infections in the old* exhibit certain peculiarities, including (1) tendency to early collapse because of cardiac failure or failure of the vasomotor or respiratory centers in the medulla, (2) frequency of respiratory complications like pneumonia or capillary bronchitis because of increased rigidity of the thorax, senile emphysema, or stasis in the pulmonary circulation, (3) early cerebral manifestations (delirium, disorientation, coma) because of cerebral atherosclerosis, of lessened resistance of nerve cells to toxins, and of low blood pressure, (4) often evidences of diminished reaction-capacity to infection as seen in low rather than high fever, slight leukocytosis, and prolongation of convalescence, and (5) frequently, absence of any acute splenic enlargement. The local symptoms of infections such as pneumonia and meningitis are often less marked, too, than in earlier life.

Since nearly half of all old people die as a result of some disorder of the circulatory system, the management of

myocardial insufficiency merits especial consideration in any discussion of the senile patient. The physician attending the old should be ever on the alert for symptoms like dyspnea, edema, and other evidences of circulatory enfeeblement; early recognition is important not only for the prevention of outspoken cardiac decompensation but for the avoidance of uremic intoxication and of cerebral softening so prone to occur in old people whose renal arterioles or cerebral arteries have suffered damage. Many writers warn against giving digitalis preparations to old people, and certainly caution should be observed in using them, particularly when symptoms of heart block, of angina pectoris, of aortic aneurysm, of retinal hemorrhage, of cerebral hemorrhage or embolism, or of severe gastrointestinal disturbances (especially diarrhea) have been present. Nevertheless, I still regard digitalis as a most valuable remedy in old age for the support of the heart muscle after it has begun to fail, especially if caffein sodium benzoate or caffein sodium salicylate be used with it. The particular preparation of digitalis administered is of less importance than the physician's experience in its application. In acute myocardial insufficiency, camphor is, also, a valuable drug. Recently, the combined use of insulin and glucose in the treatment of failing heart in both old and young patients has been coming into vogue. Rest should of course be increased, but, whenever possible, the older patient should be allowed to sit in a chair at intervals, for continuous bed rest has its special dangers for the aged. A few days of Karrell's milk diet, fol-

lowed by a simple cardiac diet of five small meals with restriction of the total fluid intake to 1500 c.c. or less, should be ordered. A daily bowel movement should be arranged for, either by means of mineral oil, psyllium seeds, compound licorice powder, a small dose of saline laxative in the early morning, or, if necessary, by the use of enemata or glycerine suppositories. Gentle general massage daily is advisable but the forms of hydrotherapy and of heart gymnastics resorted to for younger cardiac patients are best avoided in the treatment of the old. Provision should also be made for sound sleep at night by prescribing, where necessary, some barbitol derivative, but never chloral preparations; if there be marked nocturnal restlessness, codeine or a small hypodermic of morphine may be given at 9:00 p.m. though caution in the use of morphine in older people is, as everyone knows, important. If diarrhea should develop, it may be necessary, temporarily, to stop digitalis therapy and to administer calcium carbonate, salicylate of bismuth, or tannalbin until the diarrhea is checked. After the signs of circulatory insufficiency have been made to disappear it is well to keep up chronic digitalis therapy for a time. I usually give a half grain of powdered digitalis leaves with $7\frac{1}{2}$ grains of theobromine sodium salicylate thrice daily, after eating, for three weeks out of each month, provided gastrointestinal disturbances do not appear. When edema is marked, we dare not purge or sweat the patient, but rather make use of salt-poor diet and of diuretics like thecin by mouth or the enphyllin by suppository in ad-

dition to digitalis, diet, and rest. Many use calomel to promote diuresis, but I prefer to do without it in the treatment of old people. When there is bradycardia with tendency to heart block (Stokes-Adams syndrome), digitalis and strophanthus preparations should be shunned, though atropine is indicated, and caffein and theobromine preparations may be used as vasodilators; in the syncopal attacks, a handkerchief upon which a few drops of amyl nitrite have been sprinkled may be placed over the face for inhalation in the hope of cutting short the attack. Old people who suffer from heart block or from angina pectoris should have with them a small vial of nitroglycerine tablets, placing one on the back of the tongue when needed.

Of the killing diseases of old age, *pneumonia* (lobar or lobular) ranks second to circulatory disease; Dr. Osler used to speak of it as "the old man's friend". Senile lobar pneumonia is often of asthenic type (without initial chill, herpes or pain), with relatively low temperature and without marked leukocytosis. The urine is usually diminished in quantity and in chloride-content. The physical signs are often indefinite and when the existence of pneumonia is suspected, roentgenograms of the chest are most helpful in diagnosis though difficult of application unless the patient happens to be in a hospital when the attack occurs. The mortality is notoriously high. If the patient recovers, the termination is more often by lysis than by crisis. In treating pneumonia in a senile patient, we have to rely chiefly upon general measures, supporting the heart and vasomotor center by cau-

tious administration of digitalis and caffein sodium salicylate, giving inhalations of oxygen, using luke-warm compresses or sponging with alcohol and water (taking great precautions against the chilling of the patient), and paying due attention to skilful nursing, diet, elimination, and provision of fresh air. Immune sera should not, in my opinion, be used intravenously in the treatment of pneumonia in old people.

THE HYGIENE OF LATER LIFE AND THE QUESTION OF REJUVENESCENCE

Relatively few persons have a "physiological" old age; what has been designated as "normal" or "biological" death at ninety or one hundred (attributed to the wearing out of the energy units of some essential organ, most often in the form of simple senile atrophy of the heart muscle, in the course of the "major involution") is only rarely observed, for most people succumb long before the end of the maximal span for the species, either because of harmful environmental influences, or of inherent pathological defects.

It is the task of our profession to search for both the extrinsic and intrinsic causes of "pathological" old age and to educate the public as to possibilities of preventing it, or of, at least, deferring it. In attempting to solve the problem, we should keep ourselves free from the illusion that we can transcend the limits of the possible. No human organism can live longer than the potential period set by the energy-charge of the fertilized egg-cell from which it starts. The human individual must die, if for no other

reason than that this energy-charge must, during life, gradually undergo exhaustion; the human race continues because its germ-plasms receive renewals of energy-charge from generation to generation. In how far the exhaustion of the energy-charge during individual life is related to specific growth stimuli, to specific growth inhibiting factors or to both we do not yet know. Many hypotheses have been advanced with regard to changes in the blood serum and in the physical-chemical equilibrium in the body, to the accumulation of toxic products, and to endocrine disturbances; but, thus far, no hypothesis has found enough support to gain full acceptance.

Medicine has made real progress in the control of the extrinsic factors that prevent "physiological" old age and lead to death before the end of the possible span of life. The average longevity of the human being has been practically doubled since 1800 through the discoveries of curative and preventive medicine and earnest attempts to apply them. Average longevity may, doubtless, be somewhat further increased by an extension of environmental control. We have not yet reached the limits of the possible in the protection of human beings from errors of diet, faulty elimination, insufficient fresh air, physical and mental over-activity and under-activity, and the manifold pathological influences of temperature, light, electricity, mechanical forces, chemical action, infection, and the economic, the psychic, and the social surroundings. This work of protection should be enthusiastically supported with the goal of the theoretically preventable ever in mind. But

we must not forget that it is life expectancy at birth and in the earlier decades that has been increased, whereas expectancy at fifty has been increased very little in the past 100 years and average expectancy for persons of sixty and seventy has, as I have said, been falling.

Progress in the prevention of the intrinsic factors of disease and of premature death due to faulty germ-plasms has been less marked. The world has been slow to recognize and apply the possibilities of a practical eugenics that could, by a breeding-out process, improve the qualities of the germ-plasms from which human beings start. Human nature is, in a way, in conflict with the rest of Nature, and our concern for the human individual is to a certain extent antagonistic to the interests of the human race and of human society as a whole. Our humanitarian impulses compel us to do all that we can to prolong the lives not only of the strong and the "fit" but also of the weaker and the "less fit", so that many of the latter who would otherwise have died early survive to the reproductive period and transmit their faulty germ-plasms to their offspring. It can scarcely be expected that heredo-familial diseases and constitutional defects can be lessened without genetic control. We know a host of these harmful genetic influences now. Any physician who has carefully studied the genealogical records of many families must have been impressed with the significance of both dominant and recessive Mendelian traits for the incidence of disease and for the shortening of life. It is a sad fact that early arteriosclero-

sis, cancer, diabetes mellitus, cerebellar ataxia, manic-depressive psychoses, and dementia praecox are especially prevalent in certain families. Even tuberculosis is not wholly a matter of exposure to Koch's bacillus; the constitutional disposition to disease plays a great part in the incidence of and lack of resistance to this and other infections as well as in the occurrence of the more obviously heredo-familial diseases and the mortality due to them. Longevity itself is undoubtedly dependent in part upon exquisitely inheritable components. From what I have said it will be sufficiently obvious that hygienic measures directed toward the increase of the number of old persons that are healthy must, of necessity, give due attention to both genetic and environmental factors.

In the few minutes that remain, may I make brief reference to the special hygiene of later life and also say a word with regard to "rejuvenescence".

Periodic health examinations are valuable for persons over fifty-five or sixty as well as for those who are younger, in order that habits that are faulty for the time of life may be corrected, that any infectious processes present may be brought under control, and that the mind as well as the body may become adjusted to the march of the years. Persons over sixty and especially over sixty-five should sedulously avoid over-exertion, either bodily or mental. More physical rest and fewer hours of mental work may be indicated. Though the body should be regularly exercised, this exercise should be gentle and if any new form be taken up training in it should be grad-

ual. Doubles at tennis are then better than singles and nine holes of golf probably better than tennis. Gardening is a source of joy for many older people. Violent exertion of any kind and undue haste should be forbidden. When the time approaches for the lessening of the strain of occupation, it should be foreseen and the reduction should be made by degrees rather than suddenly. All too often an abrupt retirement from business or professional life has disastrous effects. The rate of progress of the reduction of activities should be individualized, for the rate that is wholesome may vary greatly in different persons. The main thing is "to take in sail" at the right time and gradually. The use of tobacco in reasonable amounts may be permissible, though patients who are developing arterial diseases (hypertension, angina pectoris, or intermittent claudication) may do well to abandon the use of it entirely.

In countries in which the use of alcohol is not prohibited, a little wine or beer or an occasional cocktail, a glass of whisky and water, or a liqueur may be much appreciated by older persons and be beneficial rather than harmful, though any excessive use should be discouraged.

Water-drinking should be regulated; a glass or two a half hour before eating will suffice, whereas an excessive intake of water throws unnecessary strain upon the heart.

A much smaller intake of food than in earlier life is desirable for older persons; after fifty-five, one should each year eat a little less. The meals should be small and should consist of simple, easily digestible foods, the

caloric intake being adjusted to the caloric needs. In general, less meat and fats should be eaten than in youth, and foods that cause gaseous indigestion, as well as rich and highly spiced foods of all sorts, should be taboo. Meals should be eaten slowly; the food should be thoroughly masticated but "Fletcherism" is unnecessary. Five small meals are better than three large ones. Breakfast may consist of milk, cereal, a soft boiled egg, coffee or tea, and a little marmalade with toast or a roll; if fish be taken at breakfast, it should be fresh, not salt or smoked. In the mid-forenoon, a glass of milk, an egg, or a cup of soup or a cracker may be eaten. The principal meal should be taken near the middle of the day and may be composed of soup, a small portion of boiled or roast meat, chicken, fish or oysters, two delicate green vegetables, and a little stewed fruit or some cottage cheese and a demitasse of coffee; if the patient be not too heavy, a little mashed or baked potato, or rice, or macaroni may be added. In the afternoon, a cup of tea with a cracker or a little toast may be eaten. The evening meal should be small and devoid of meat; eggs in some form with bread and butter or toast and fresh salad, or (instead of eggs) milk, may be followed by a little stewed fruit or a simple pudding. A small cup of decaffeinated coffee will do no harm.

Older patients should weigh themselves weekly and keep a record of the weight in order that the physician may form a right judgment regarding the optimal caloric intake.

Regular bathing habits should be maintained, but caution should be ob-

served regarding excessively cold or hot water for the bath. Gentle calisthenic exercises in the morning are often advantageous; J. P. Müller's system in which part of the exercises are taken before the bath, and part (with skin rubbing) after the bath, are found helpful by many.

Constipation should be carefully avoided; when it is marked, one must make sure that no enterostenosis is developing. The fruits and green vegetables of the diet recommended together with regular exercise will usually suffice for regular bowel movements, though some persons may require acidophilus milk or a little mineral oil or psyllium seeds in addition. If laxatives are used, they should be mild and should be changed from time to time. An occasional enema may be desirable but I am opposed to the enema habit that so many adopt.

Summer vacations should be spent at the sea or, if preferred, at medium altitudes, where there are forests or shaded walks; very hot and very dry places are best avoided. Winter vacations may be spent in the South or Southwest, especially if there be any tendency to bronchial catarrh.

The dying down of sexual desire and potency in later life seems to be one of Nature's safeguards for older men, especially for those who have had bradycardia, dyspnea, or symptoms of angina pectoris. In any case, great moderation in sexual indulgence is advisable, remembering Wordsworth's saying that "Love in old folk a great damage is!" Much has been written of late of "rejuvenescence" by means of Stinch's operation or by administration of endocrine products.

The evidence favors the view that any rejuvenating effects obtainable are but transitory; there may be a temporary "re-erotization", but this is of doubtful value and not devoid of danger to the older man.

The mental state of older persons should be carefully watched. The physician who undervalues psychotherapy in the management of patients over sixty makes a great mistake. All too many persons, when they first become conscious of the fact that they are growing old become pessimistic, complain that the world is going to the "bow-wows", declare that "life is over" for them, become negligent of personal appearance, tidiness, and social duties, yield to their apathy and diminished interests and become hypochondriacal—attitudes that undoubtedly hasten the aging process. A few go to the other extreme, vehemently deny any change in their physical or mental powers, and, as a sort of overcompensation for the flagging of their powers that they have really felt, tend to become overactive and to outvie even younger people in their lust for pleasures and their enthusiasms. But when the shrewd physician who has observed many older persons detects the premonitory involutional symptoms, he will do all that he can to guide his patients along the right paths, discouraging undue "let-up" on the one hand and excessive epicurean "let-loose" on the other. The older person who is wise will frankly recognize that there are unpleasant features of age that cannot be abrogated; but he will cultivate a philosophy that is based upon the realities of the life of the human individual and of the human species.

He will cling to the fact that every age of life has its own blessings and is good for its own sake, though he will hope that he may be lucky enough to escape from life before "second childhood". As Longcope has recently emphasized, the mere extension of life for "helpless doddering wrecks of humanity" is of but little value; he approves of Stevenson's attitude when he asked the question, "Does not life go down with better grace, foaming in full body over a precipice, than miserably straggling to an end in sandy deltas?" Older persons ought to meet the restrictions that age imposes with

courage and common sense and should enjoy to the full the compensations that later life brings—"honor, love, obedience, troops of friends". Like Macbeth, they will determine that "the mind I sway by and the heart I bear shall never sag with doubt nor shake with fear". And as long as possible, they will cultivate their hobbies and continue to participate in the intellectual pleasures of music, art, literature, and science. Thus living, one may, it is true, become old, but he will at least have gone far in the art of bearing age aright.

REFERENCES

- BARKER, L. F., and SPRUNT, T. P.: Degenerative diseases; their causes and prevention, 1925, Harper Bros., New York.
- BAUER, J.: Die konstitutionelle Disposition zu inneren Krankheiten, 3 ed., 1924, J. Springer, Berlin.
- COUNCILMAN, W. T.: The conditions presented in the heart and kidneys of old people. Contributions to medical and biological research dedicated to Sir William Osler, New York, 1919, ii, 918-928.
- CRITCHLEY, M.: The neurology of old age (Goulstonian lecture), *Lancet*, 1931, i, 1119-1127; 1221; 1331.
- FERGUSON, J.: Problems of old age, *Trans. Royal Med. Chir. Soc., Glasgow*, 1930, xxiv, 1-26.
- HALL, G. S.: Senescence, the last half of life, 1922, D. Appleton and Co., New York.
- JENNINGS, H. S.: Life and death, heredity and evolution in unicellular organisms, 1920, Badger, Boston.
- LOEB, J.: Natural death and the duration of life, *Sci. Monthly*, 1919, ix, 578-585.
- NASCHER, I. L.: Geriatrics, 2 ed., 1916, Blakiston, Philadelphia.
- PEARL, R.: Span of life and average duration of life, *Nat. Hist.*, 1926, xxvi, 26-30.
- PEARL, R., and RAENKHAM, T.: Studies on human longevity; constitutional factors in mortality at advanced ages, *Human Biol.*, 1932, iv, 30-118.
- LONGCOPE, W. T.: Methods and medicine, *Bull. Johns Hopkins Hosp.*, 1932, 1, 4-20.
- ROLLESTON, H.: Some medical aspects of old age, 1922, Macmillan, New York.
- RUNGE, W.: Die Geistesstörungen des Greisenalters. In: BUMKE's Handbuch der Geisteskrankheiten, Berlin, 1930, 8:Spez. Teil 4, 597-664.
- SCHLESINGER, H.: Die Krankheiten des höheren Alters und ihre Heilung, 2 vol., Wien u. Leipzig, 1914-1915, A Hölder.
- THEWLIS, M. W.: Geriatrics, 1924, C. V. Mosby, St. Louis.
- WARTHIN, A. S.: Old age; the major involution, 1930, Hoeber, New York.
- WILLIAMS, C.: Opportunities for improving the health of the aged in the administration of the Massachusetts old age assistance law, *New Eng. Jr. Med.*, 1931, ccv, 955-963.
- WILLIUS, F. A.: The heart in old age; a study of 700 patients seventy-five years of age and older, *Am. Jr. Med. Sci.*, 1931, clxxxii, 1-12.
- WORCESTER, A.: The care of the dying, *Jr. Med.*, 1932, xiii, 62-70. Also in: *South. Med. & Surg.*, 1932, xciv, 497-499.

The Rôle of Bacteria in Allergy, with Special Reference to Asthma*

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AS early as the beginning of the present century the late Victor C. Vaughan¹ already had an adequate understanding of the problems of bacterial sensitization. This eminent biochemist maintained that bacteria, although morphologically simple in structure, are correspondingly complicated in their chemistry and comprise in particular a group of highly complex proteins. His insight into the minute chemistry of bacteria is further evidenced by his account of one or more carbohydrate components which he regarded as intimately linked with the large nucleoprotein molecules. He concluded that these constituents could readily be split apart by dilute acid or alkali, but better by 2 per cent solution of caustic soda in absolute alcohol. The resulting protein nucleus set free was found to be non-specific and poisonous, while the other component, largely carbohydrate, was highly specific but non-toxic.

The further development of this important phase of bacteriology diverges along two general lines. One of these concerns bacterial variation from the smooth, or S-type, into the rough, or R-type, with relative loss of virulence.²

The other includes the advances in knowledge of the bacterial antigens found in the brilliant and detailed reports of Avery and his colleagues, Zinsser and his colleagues, Lancefield and others, who, working with various pathogenic organisms, have isolated two distinct fractions—a nucleoprotein which is antigenic but not highly specific and a carbohydrate which lacks antigenic power but is definitely specific.

Dochez and Avery³ in 1917 described a type-specific soluble substance which they had isolated from broth cultures of pneumococcus, and which they decided was a secretory product of the bacterial capsule. Zinsser and Parker⁴ in 1923 corroborated Dochez and Avery's result with pneumococcus and reported similar soluble specific substances obtained from cultures of tubercle bacillus, *Staphylococcus aureus*, influenza bacillus, and typhoid bacillus. The same type of specific soluble substance has been isolated from cultures of Friedlander's bacillus,⁵ yeasts,⁶ *Streptococcus viridans*,⁷ hemolytic streptococcus,⁸ *Meningococcus*,⁹ and members of the coli-typhoid group.² These various substances are admittedly of the same nature and apparently resemble that obtained by Pick¹⁰ as early as 1902. It is not necessary to recount in detail the prop-

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erties of these soluble bacterial products. Full descriptions are to be found in the reports of Avery and Zinsser and their co-workers.

Mention should be made of other soluble antigens and corresponding antibodies recently attributed to the pneumococcus. Sabin¹¹ found that Type I antipneumococcus serum, after the total precipitation of the antihydrate precipitins, retained a definite amount of its type-specific protective action which was not neutralized by additional SSS ("specific soluble substance"). It could be absorbed, but only by the homologous virulent pneumococci. Enders¹² reported in the autolytic products of pneumococcus Type I a substance distinct from SSS but reacting specifically with its homologous antiserum. In weakly alkaline solution this is destroyed by boiling but not in acid solution. It resists peptic digestion and appears to belong, like SSS, to the group of haptenes. Such findings suggest the possibility that bacteria contain in their infinitesimal makeup an indefinite variety of specific protein compounds which are capable of acting as antigens and of inciting the formation of antibodies in the animal host.

It may not be out of place here to attempt a tabulation of various bacterial effects which have been described.

1. Foreign non-specific protein action has been reported by Miller¹³ and others, and may be regarded as having some importance. Coca and his collaborators,¹⁴ in their comprehensive text on allergy, conclude on inadequate premises that the idea has been "relinquished that vaccine treatment is a specific form of therapy". In this

presentation I shall admit the existence of such a procedure as protein shock therapy but at the same time draw a distinction between this type of treatment and the highly specific vaccine therapy employed by the Dicks and Dochez in scarlatina and by various workers in bacterial asthma. Topley and Wilson¹⁵ presented at length the experimental evidence against the reputed importance of the non-specific factors. They concluded that there is no evidence that any non-specific stimulus can cause the appearance of any of the known serum antibodies. While there is some evidence that such non-specific stimuli may cause an increase in any of the normal antibodies or a secondary rise in titre when administered after the effect of the preliminary specific immunization has reached its zenith or begun to decline, the responses falling within this category are irregular or trivial and never comparable to those following the reinjection of the specific antigen. Pilot¹⁶ and others, working with the skin reactions in man with staphylococci, found that of fifty-six patients suffering from staphylococcus infection 89 per cent reacted positively and often more violently than normal persons. From this it might be inferred that mere infection is identical with sensitization. On the other hand, Pottenger,¹⁷ referring to infection with another organism, calls attention to the important conception that a relatively greater hypersensitivity of the cells is likely to be present in the earlier and more active stages of the infection than later. Others¹⁸ have reported anaphylactic and even asthma-like symptoms in guinea pigs from repeated intravenous and intratracheal

injections of green-producing streptococci. The results, while not very striking, were said to resemble in many respects the corresponding human respiratory phenomena.

2. The Vaughan and Friedberger¹⁹ split products must be considered as possible toxic factors in any infectious disease but accentuated in their importance in hypersensitive states.

3. Production of histamine-like substances with resulting bronchospasm by bacteria of the *B. Friedlander* group has been reported by Knott and Oriel and is described in the Report of Research at the Asthma Clinic of Guy's Hospital for 1928-1930. Harkavy²⁰ had found a spasm-producing substance in the sputum during asthmatic attacks which was absent during the free interval. These findings are of interest in comparison with the observation of Koessler, Hanke and Sheppard²¹ that histamine could be produced in the intestinal tract by various members of the coli-typhoid group.

4. The nucleoprotein and SSS fractions of Avery and others have already been mentioned and the research of Sabin and of Enders suggests the probability of a multiplicity of specific soluble products of bacteria.

5. The Arthus²² phenomenon is a special type of accelerated allergic response in rabbits and other animals. After several daily inoculations of a foreign protein without noteworthy effect, subsequent inoculations of the same type produce a hard aseptic infiltration which persists for days or even weeks.

6. The Schwartzman²³ phenomenon is an unexplained skin response to bac-

terial filtrates and is elicited as follows: The sterile filtrate of the broth culture is injected into the skin of rabbits and after twenty-four hours a suitable amount of the same filtrate is injected intravenously. This results within four or five hours in a hemorrhagic necrotic swelling of the originally injected skin sites. This phenomenon has been produced with cultures of several different bacteria even if filtrates from entirely unrelated bacteria were used for the skin-preparatory and injury-producing factors respectively. The skin-preparatory substance is, however, of a specific antigenic nature and neutralization of either the skin-preparatory or injury-producing factors is possible only through the use of homologous sera.

7. The Dick²⁴ toxin differs from the SSS of Avery in that, although heat resistant, it gives rise to a specific antiserum.

8. The observations of Touart²⁵ and others that old quiescent vaccine inoculation sites are relighted by subsequent inoculations of the same vaccine in a different location deserve comment. Patients have repeatedly called my attention to this phenomenon.

These various manifestations of bacterial action have been listed to call attention to the multiplicity of antigens and effects coming from bacterial metabolism and the corresponding complexity of reactions on the part of the host. It is entirely conceivable that some of these specific and non-specific bacterial agencies enact an appreciable part in the pathogenesis of infectious asthma and other hypersensitive clinical states attributable to bacteria.

SENSITIZATION TO BACTERIA

It is a matter of common observation that certain cases of asthma, rhinitis, migraine, urticaria and other allergic conditions are unexplainable on the basis of reaction to the ordinary foods and inhalants. It is equally evident that the causes of most of these must be sought in the infectious processes within the body. In general, the workers in this specialty of medicine have divided their cases into bacterial and non-bacterial, or categories which are equivalent. The only matter of disagreement concerns the question of specificity or non-specificity in the bacterial causes.

There can be no reasonable doubt that bacterial infection may, by its mere presence in the bronchial tree, cause irritation of the vagus nerve endings or bronchial musculature directly and thus furnish the *modus operandi* of the bronchospasm and attendant exudation and edema of asthma. In accordance with this many authorities maintain that vaccine treatment in asthma is nothing more than foreign protein shock therapy. This same line of reasoning applies also to the protein split product theories of Vaughan and of Friedlander, or to the bacterial histamine-like bodies of the Guy's Hospital Staff. It is entirely possible that any one or more of these non-specific chemical factors may be operative in certain instances. The pioneer research of Vaughan has indicated that any bacteria, including the relatively avirulent *B. coli* group, have an inherent toxicity for the animal organism.

We are, however, equally concerned with the more specific effect of the pathogenic microorganisms on the hu-

man subject. I refer to those manifestations of bacterial action which are characterized by definite sensitization phenomena.

Several difficulties present themselves at once. The first of these is the supposed discrepancy between human allergy and animal anaphylaxis, owing to the frequent failure to obtain passive sensitization of animals by injections of allergic sera. I am inclined to agree in this regard with Zinsser²⁶ that we should not neglect the basic principles of hypersensitiveness in favor of discrepancies which represent gaps in our experimental knowledge rather than fundamental differences of principle. Another and more formidable obstacle lies in the extreme complexity of the bacterial antigens and antibodies as compared with those of the simpler coagulable proteins.

Bacterial anaphylaxis has been thoroughly established as a scientific fact. "Active and passive sensitization may be induced with bacterial antigens, as determined by the occurrence of anaphylactic shock (Rosenau and Anderson 1907, Kraus and Doerr 1908, Holobut 1909, Kraus and Admiridzibi 1910, Zinsser and Parker 1917, Tomcsik and Kurotchkin 1928), or by Dale's technic with the isolated uterus (Zinsser and Parker 1917, Zinsser and Mallory 1924, Tomcsik and Kurotchkin 1928). The reactions are specific and desensitization can be demonstrated.

"Sensitization to bacterial antigens cannot, however, be produced with the same ease and certainty, as in the case of horse serum or egg-white. A single injection of bacteria, or bacterial extract, frequently fails to produce any

demonstrable sensitization, and the most successful results have been obtained by those workers who have employed repeated small injections of antigen for sensitization, followed by an interval of three weeks or so".¹⁵

Zinsser²⁶ has cited convincing instances of laboratory sensitization with tuberculin. The evidences of bacterial anaphylaxis are, however, relatively slight in degree. Zinsser and Tamiya²⁷ attribute this limited formation of antiprotein antibodies, and consequently of true anaphylaxis, to the fact that coagulable protein, though present to a slight extent in bacterial extracts, does not predominate in the bodies of the bacteria. The bacterial hypersensitiveness which concerns us in asthma and other allergic conditions is essentially different from the anaphylactic phenomenon. Its development is usually dependent upon the presence of the whole bacteria in the organism and appears to be related to the nucleoprotein-carbohydrate combination of Avery, Zinsser and others. The complex chemistry of the bacterial cell body contains other substances which may well assume importance in sensitization phenomena when their properties have been more thoroughly studied.

CLINICAL OBSERVATIONS

Classification of Allergic Cases. In the absence of a better classification I have grouped my asthma cases according to their causes, into (a) non-bacterial, (b) bacterial, and (c) mixed bacterial and non-bacterial. Group (c) represents the experience gained from extensive testing with foods and dusts. Reactions to them, even though nu-

merous and definite, imply merely a sensitiveness of the skin to the individual allergen and do not in any sense preclude a coexisting bacterial sensitization which may be the underlying process. Many striking instances of this class might be cited.

The routine procedure in my practice is to test the dermal reactions to the foods and dusts with which the patient comes in contact. Regardless of reactions or their absence the possibility of bacterial causes is investigated. A careful history of previous outbreaks of infection, especially in their relation to asthmatic attacks and to seasonal variation, is of help. Certain laboratory procedures, such as the leukocytic and eosinophilic counts, the sedimentation velocity of the blood, the character of the sputum and the results of proper culturing, when combined with physical inspection and the diagnostic employment of iodides and other medication, usually give a fairly accurate determination of the type of asthma.

The choice of material for culture is as important as the technic. Sputum, and in particular Curschmann spirals, are washed in sterile saline, ground in a mortar with sterile sand and cultured with addition of the patient's blood or serum in pour plates and brain broth, also at times streaked on agar and Sabouraud's medium. The blood agar pour plates made on a decimal scale of dilution enable a count of the various bacteria of the sputum. These include in order of frequency *Streptococcus viridans*, hemolytic streptococcus, non-hemolytic streptococcus, *Staphylococcus aureus*, pneumococcus, and others of less importance. The

number of organisms in 1.0 c.c. of sputum ranges from a few thousand to many millions.

We are probably concerned equally in asthma with the intestinal flora. As stated by Zinsser²⁶ sensitization of the lung does not necessarily imply that the hypersensitive state is relatively more marked in the lung tissues. In my experience culture of the feces carried out according to a rigid technic²⁸ which inhibits the growth of the intestinal gram-negative organisms has yielded definite results in asthma and other allergic conditions. By this method the normal individual and the non-bacterial sensitization case usually give a negative or negligible culture, while the subject with bacterial allergy will, in the majority of instances, give a growth of pathogenic intestinal bacteria ranging from 100,000 up to many millions from each loopful of stool plated out. In one case it was estimated that one loopful of stool contained 127,000,000 green-producing streptococci. The organisms encountered are, in order of frequency, *Streptococcus viridans*, *hemolyticus*, *non-hemolyticus*, *Staphylococcus aureus* and rarely other organisms.

Many of these asthmatics showing a preponderance of pathogenic cocci in the feces have complained of colitis with loose movements and sometimes with blood and mucus in the stools, especially at the time of asthmatic seizures. Probably a still greater percentage have suffered with constipation. A minority, even in the presence of extreme infestation of the bowel by pathogens, complain of no irregularity in the matter of movements. The presence of a high grade infestation, with

or without noticeable clinical disturbance, is to be regarded as a potential cause of asthmatic paroxysms.

In addition to the almost routine culturing of the sputum and feces, cultures are made in selected cases from the sinuses, tonsils, teeth, and other foci. A variety of organisms is obtained.

In other allergic conditions than asthma, including bacterial rhinitis, eczema, dermatitis, urticaria, migraine, and certain rheumatic and ocular conditions, culturing has often been carried out according to methods suited to the condition. Particularly illustrative of the broad application of the principles of bacterial sensitization here enunciated are several cases of iritis referred to me for study. Two out of four such cases treated with streptococcus stool vaccines have shown diverticulosis of the colon on X-ray of the abdomen. Strangely enough, these two with diverticulosis have apparently recovered under vaccine treatment, while the others are still refractory. This subject will be presented in detail in a separate report. Infection in relation to eczema will also be reported separately.

Preparation of Vaccines. In an effort to obtain vaccines which should contain the specific principles of the causative organisms, the following types of bacterial preparation have been studied: (a) washed organisms killed at 60°C. for one hour; (b) unheated Berkefeld filtrates from brain broth cultures containing patient's serum; (c) whole broth cultures in brain broth containing patient's serum and including both the bacteria and their medium.

Each of these types of bacterial preparation has been used in a considerable series of cases for testing and treatment. All have been found specific and have been used with success in treatment. Their relative merits will be discussed following a short summary of the cutaneous reactions. In addition to these three preparations the protein fraction of thoroughly ground bacteria has, in certain instances, been obtained by precipitation with cold alcohol and tested cutaneously on patients. (Figure 1, D).

The requisites for success in vaccine treatment have been proper choice of foci for culturing, careful isolation of

the predominant organisms as determined by plate counts, and standardization of dosage by cutaneous tests and systemic reaction. It is also important to employ a type of bacterial preparation which shall include the specific causes of asthma.

Cutaneous Reactions. The reactions obtained in a series of 500 cases of asthma, including a smaller series of 232 cases studied in greater detail, lead me to agree with Thomas,²⁰ Famulener and Touart, Haibe³⁰ in Belgium and others that the reactions of intradermal tests in conjunction with the systemic effects of bacterial inoculation form the most reliable

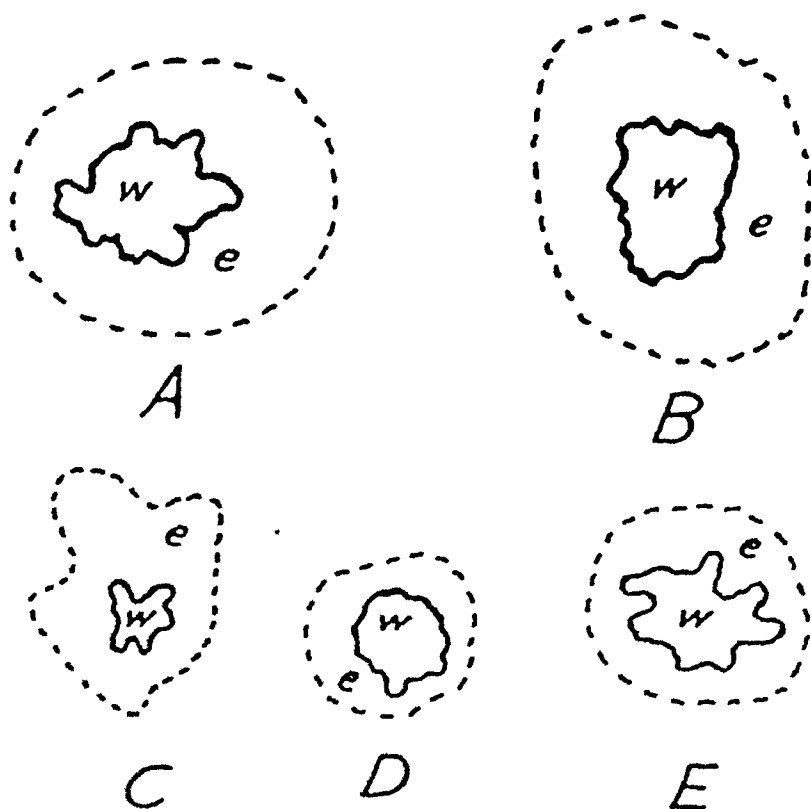


FIG. 1. Trailings of intradermal reactions to bacteria (natural size). w, wheal; e, erythema. A, immediate reaction to *Streptococcus viridans* stool vaccine in patient with earlier cases. B, immediate reaction to *Streptococcus viridans* stool vaccine in asthmatic patient. C, spontaneous four reactions to hemolytic streptococcus showing small wheal and erythema. D, early reaction to purified protein from *Streptococcus viridans* of patient with asthma. E, reaction to stool vaccine organisms as B. (The bacterial reactions are larger than the protein reactions.)

guide to vaccine therapy. It seems advisable to test the reactivity of the skin to the separate bacterial preparations—washed bacteria, filtrate, and whole culture—and to study the use in treatment of those which react.

In evaluating the reactions, most authors are of the opinion that the immediate wheal and its surrounding erythema are of non-specific origin due to the foreign material in the medium and the purely toxic effect of the bacterial extracts. In general my results support this contention. Having repeatedly tested patients with bacterial products and with the homologous sterile medium incubated under similar conditions, I can state that in the great majority of instances the medium produces an immediate intradermal reaction entirely comparable to that with the corresponding whole vaccine. In such cases the reaction must be regarded as non-specific.

Attention must, however, be called to occasional exceptions to this rule of which I shall cite only a few. Figure 1, B is from a tracing of the immediate wheal and erythema from intradermal inoculation of a *Streptococcus viridans* stool vaccine in an asthmatic four years of age. Control inoculations in normal individuals were small and lacking in pseudopodia. The twenty-four hour reaction was entirely negative, yet within ten hours following the inoculation the patient developed a severe attack of asthma. This fact, together with the favorable outcome of vaccine treatment, leads me to believe that this child's immediate reaction was of a specific nature and that it constituted the essential skin manifestation

of his bacterial sensitization. Figure 1, A represents a tracing of the immediate reaction to a *Streptococcus viridans* stool vaccine inoculation in a boy who had had canker sores in the mouth for years. Despite the absence of a twenty-four hour reaction this boy made a prompt recovery from his mouth condition and gained progressively in weight and strength. Other such instances might be cited indicating that the immediate reaction is occasionally of primary importance. To these might be added a few other cases in which a significant immediate wheal is followed by a definite delayed intradermal reaction.

As a rule, however, the characteristic cutaneous response to intradermal inoculations is represented by changes in the inoculation site occurring in ten, fifteen, or twenty-four hours, rarely later. Because of the variability in the length of this period it is advisable to make repeated inspections during the first twenty-four hours. I have even had cases of multiple inoculations in the same patient in whom certain reactions showed best at fifteen hours and later faded, whereas others were scarcely visible until twenty-four hours had elapsed.

The character of the cutaneous response is variable. The most usual type resembles that commonly seen in the Dick test and I have accordingly followed the practice of doing the latter test on the same arm as a control, particularly in connection with those cases infected with hemolytic streptococcus. At times the Dick test gives a result which agrees with that of the autogenous hemolytic streptococcus filtrate and vaccine; on other occasions

the two are at variance. A finding which is sometimes overlooked in both is the occasional appearance in fifteen or twenty hours after inoculation of a wheal followed several hours later by a reddish areola of the same size, or even much larger. (Figure 1, C). At times a deep reddish papule forms the center of the areola, especially in *Staphylococcus aureus* reactions (figure 2), and this may even have a

homologous with those found in scarlatina* or may be entirely dissimilar.

The site inoculated with washed hemolytic streptococci may react more strongly than the point inoculated with unheated filtrate from the same culture, or the reverse may occur. More often both respond about equally (figure 6).

Streptococcus viridans and non-hemolytic recovered from the respiratory



FIG. 2. Twenty-four hour reaction to intradermal inoculation of 0.02 c.c. *Staphylococcus aureus* nose vaccine of asthmatic. Note papule in center of areola.

yellowish purulent-looking but sterile apex (figure 3).

Reactions of *Streptococcus hemolyticus*, when present, are usually entirely comparable with the ordinary twenty-four hour response to the Dick test. Of interest in this connection is the observation that, in the definitely positive hemolytic streptococcus cases, the response to the Dick test may be equally erect (figure 4), or may be falling (figure 5). It seems probable that the hemolytic streptococci employed in the serum and food of allergic cases may be immunologically

or intestinal tract of asthmatics usually elicit cutaneous responses which are similar to those obtained with *Streptococcus hemolyticus*. In the case of the former groups the washed organisms, or the whole brain broth culture, usually react more strongly than the unheated filtrate (figure 7), although the reverse is occasionally true.

*In one child five years of age, apparently belonging to this group, I treated a violent asthmatic upset by intravenous injection of 200 c.c. of antiscarlatinal serum with such a prompt and gratifying result that I feel I should recommend the procedure for consideration.

Staphylococcus aureus, since it grows better in solid media, has been used in the form of emulsions of washed and heated organisms. The behavior of these following intradermal inoculation is similar to that of the streptococci except for the more frequent

bacterial capsule probably contain a predominating amount of the specific SSS haptene of Avery while the bacterial bodies retain the bulk of the less specific, but antigenic, nucleoprotein fraction. The choice of the particular cultures which enter into the vaccine



FIG. 3 Twenty-four hour reaction to intradermal inoculation of *Staphylococcus aureus* nose vaccine of dermatitis case, containing in the midst of the arcola a papule with yellow center.

production by the former of reactions having a papular or pseudopustular center. Other organisms are occasionally employed in my vaccine therapy but have not received the same detailed study as the foregoing.

The vaccines employed usually include both heat-killed bacteria and unheated filtrate. This practice is based on the assumption that the filtrate and

is, however, made on the basis of cutaneous reactions and, to some extent, of the relative preponderance of each organism in the original focus.

Having mixed together those cultures which are considered of probable importance, a trial dosage is worked out on the basis of the sensitiveness manifested by the skin and on general reactions if such occur. The usual

dilution is 1:20 or 1:50 in terms of whole broth culture, or, if several strains are included, dilutions of 1:100 or occasionally even 1:1000. By starting with a minute dosage, say 0.05 c.c., it is generally possible eventually to desensitize the individual to the bac-

error owing to personal factors in the patient such as lack of coöperation and veracity, geographical considerations, overwork, and others. The figures have, however, been collected for what they may be worth and include those 232 cases of asthma in my prac-

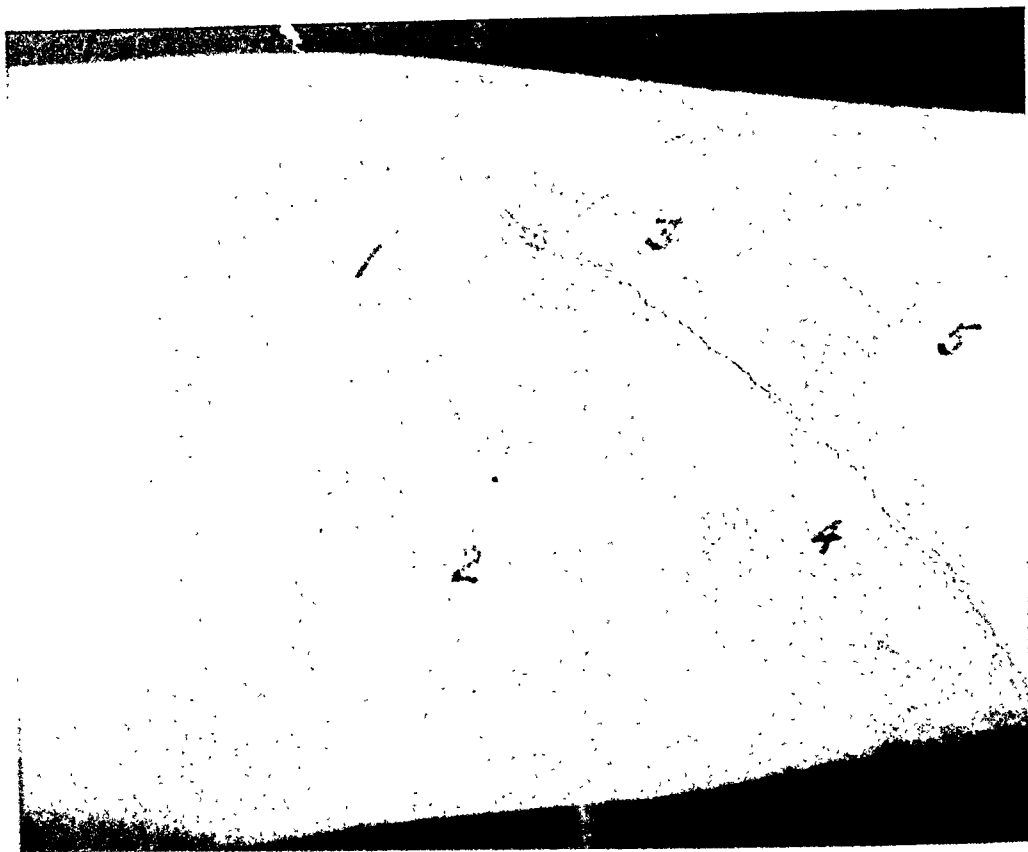


FIG. 4. Twenty-four hour reactions to intradermal inoculations of vaccines and filtrates in asthmatic patient. 1. hemolytic streptococcus sputum vaccine; 2. hemolytic streptococcus sputum filtrate; 3. *Streptococcus viridans* stool vaccine; 4. *Streptococcus viridans* stool filtrate; 5. Dick toxin.

terial antigens. When this is accomplished the dosage, and even the concentration, are increased in the hope that the individual may "pass through an allergic state into one of immunity to the same agent".¹⁰

Results of Vaccine Treatment. The results of treatment along the lines mentioned have been entirely favorable. Any tabulation of figures in this regard is subject to a great range of

tice which have been worked out in sufficient detail to permit analysis. Of these, 21 were non-bacterial and were treated on the basis of elimination or of specific inoculations against the offending foods and dusts; 94 were classed as of bacterial origin and subjected to vaccine therapy; and 117 were considered of mixed bacterial and other origin and given vaccine treatment along with suitable attention to

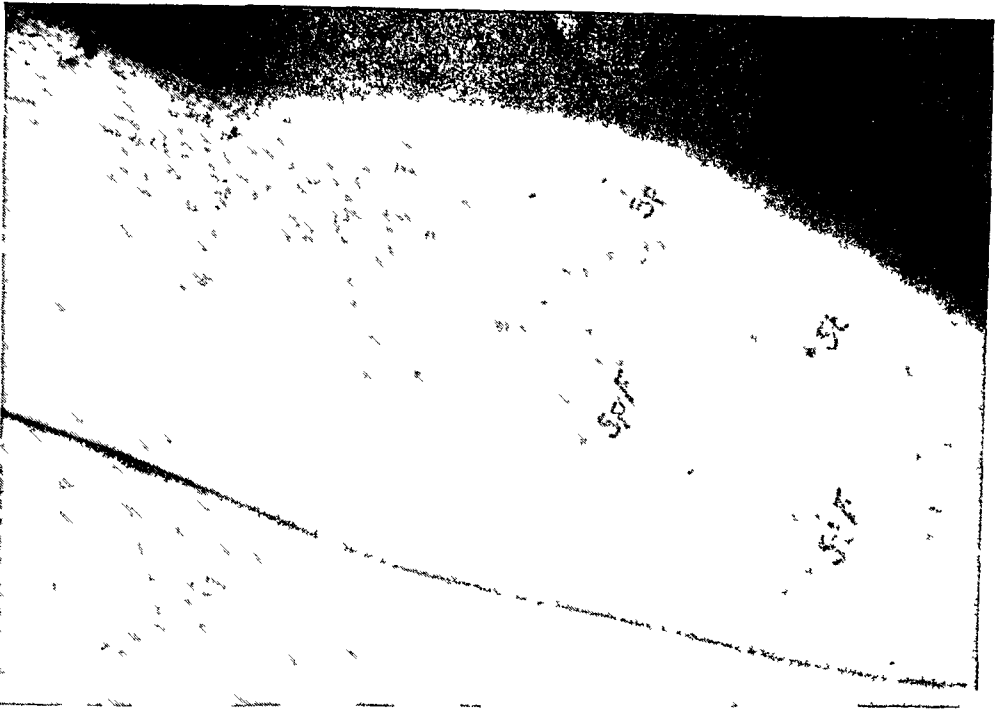


FIG 5. Twenty-four hour reactions to intradermal inoculations of vaccines and filtrates in asthmatic patient. *D.* Dick toxin, negative *Sp.* sputum vaccine, mild reaction *Sp. F.* sputum filtrate, negative. *St.* hemolytic streptococcus stool vaccine, moderate reaction *St. F.* hemolytic streptococcus stool filtrate, moderate reaction

the non-bacterial allergens. The results are best expressed in a simple tabulation.

The results in the bacterial group are almost identical with those in the other groups. In past years I have shared the prevailing American opinion that definite reactions to foods and dusts offered the only real outlook for successful asthma treatment. This feel-

ing has undergone a reversal accompanied by a corresponding improvement in results. The English insistence on metabolic and other systemic factors has wrought considerable change in our conception of asthma. The greatest single stride, however, has been a growing appreciation of the rôle of bacteria in asthma, and considerable credit for this phase of the develop-

TABLE I

	Non-bacterial	Bacterial	Mixed	Total
Cases	21	94	117	232
Complete or nearly complete relief	24%	22%	24%	23%
Moderate relief	29%	29%	38%	34%
Slight relief	19%	28%	23%	25%
No relief	5%	10 5%	3%	6%
Result unknown	23%	10 5%	12%	12%

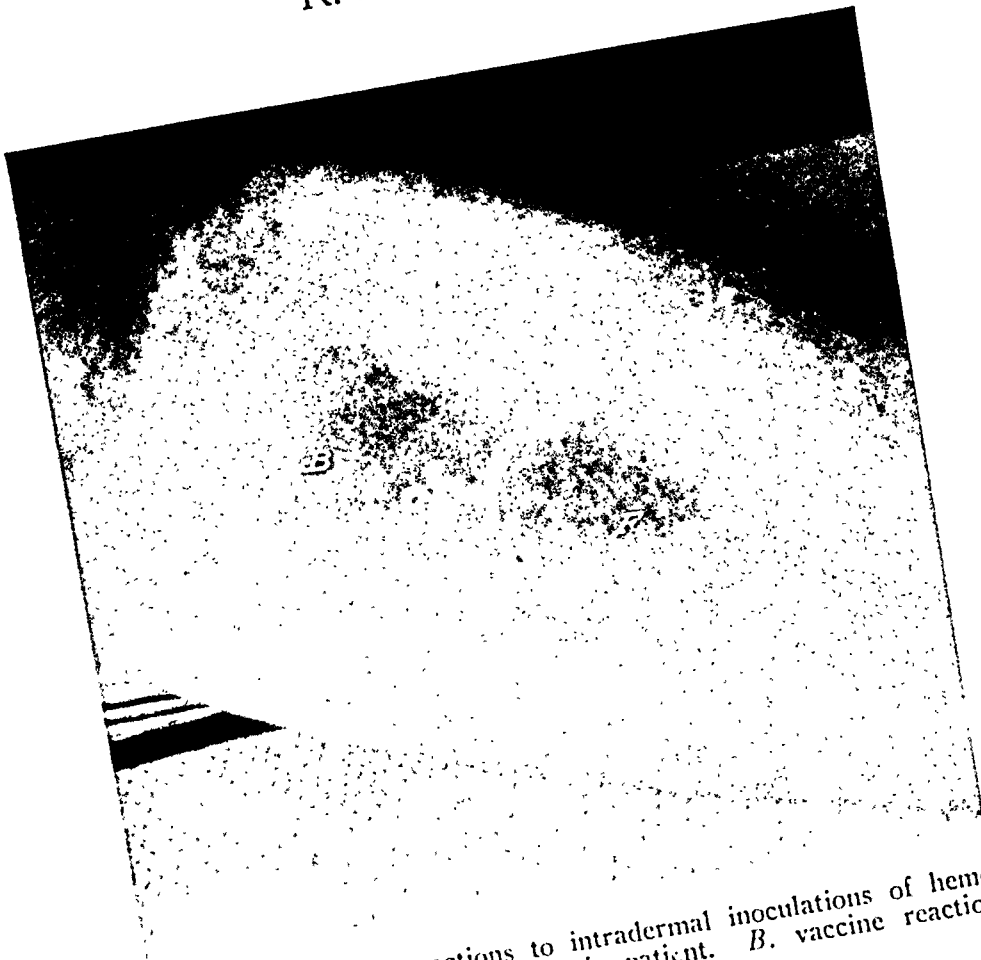


FIG. 6. Twenty-four hour reactions to intradermal inoculations of hemolytic streptococcus stool vaccine and filtrate of asthmatic patient. B. vaccine reaction; F. filtrate reaction.

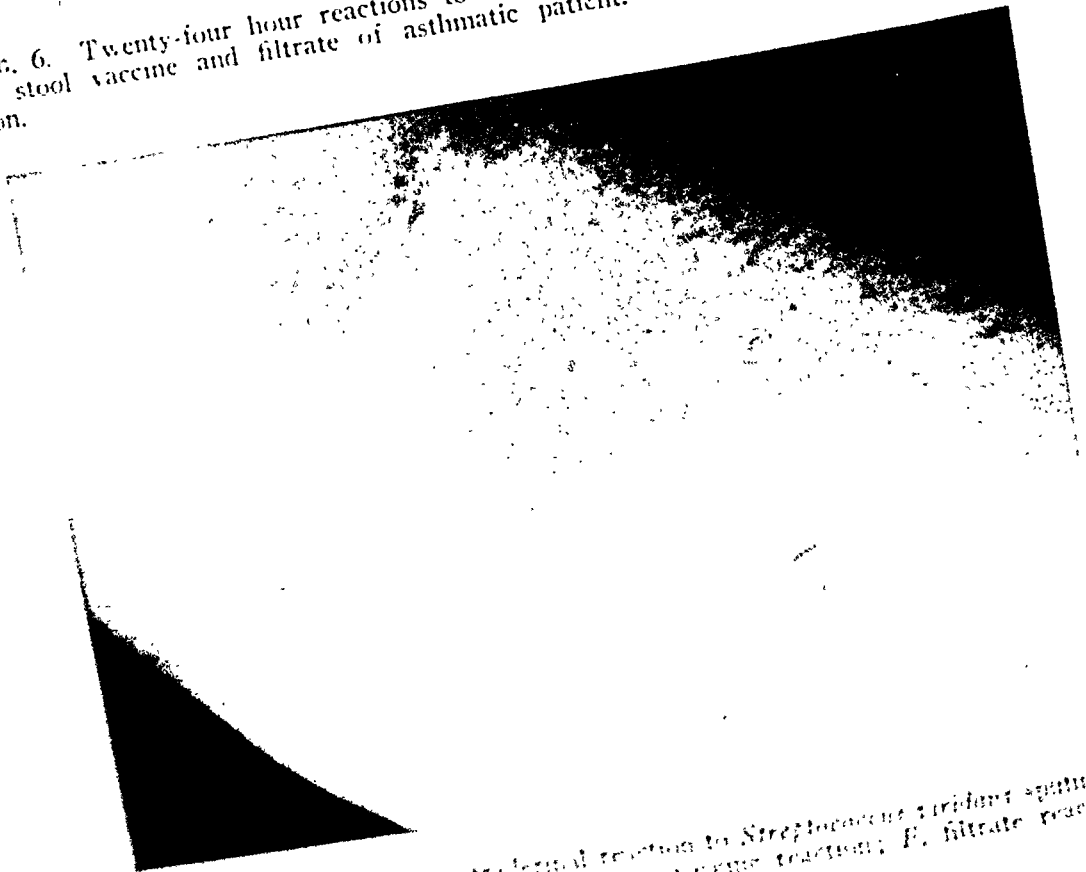


FIG. 7. Twenty-four hour reactions to intradermal reaction to *Streptococcus viridans* stool vaccine and filtrate of asthmatic patient. B. vaccine reaction; F. filtrate reaction. (x4)

ment belongs to Sir Almroth Wright³¹ and Fleming in England and to Walker³² and Thomas²⁹ and his co-workers in America. I am forced to agree with Haibe³⁰ of Belgium that too much stress has been laid on the cutaneous reactions to foods and dusts in the American reports. He considers that many of these are false reactions and that in any case they may not furnish the key to the allergy.

Of more value than any table of figures is a detailed analysis of individual cases of bacterial sensitization with records showing relative bacterial desensitization through specific treatment. I could cite many instances in which a minute intradermal inoculation of autogenous bacterial antigen has, within one to several hours, precipitated a violent paroxysm of asthma, notwithstanding the fact that a control inoculation of fully 100 times the quantity of stock vaccine has failed to produce a similar effect. Equally convincing evidence for specificity is afforded by the prompt and complete cessation of asthmatic attacks which not infrequently follows the initial intradermal bacterial inoculation of the proper size. The following is a typical example. The patient, a girl of eleven years, had had asthma continuously without any complete intermission from the age of two. At the time of her first visit she was a pitiful spectacle, in an advanced stage of emaciation, and with chest deformity of the pigeon type. Cutaneous tests proved her sensitive to grass pollens, horse epidermal extract, housedust, and many foods. Stool culture yielded hemolytic streptococcus in large numbers, and culture from the nares gave *Staphylococcus*

aureus. Repeated inoculations with minute doses of the undiluted vaccines were followed by an increase of the asthma, and the patient returned home in a worse condition than when she came to me. Several months later she returned for observation. Her first week in Portland was devoted to laboratory procedures, and no relief of her asthma accompanied the change of climate. At that time an inoculation of 0.05 c.c. of a 1:10 dilution of the original vaccine was given her and resulted in a complete cessation of her asthma for the first time in nine years. There was no return of symptoms during the following week, at the end of which she left for home. This case is cited as an example of the aggravation of symptoms which frequently follows overdosage of vaccine and the prompt relief which can result from a proper dosage. Many cases might be cited which are equally convincing and in which the relief of symptoms has lasted over a period varying from one to several years.

Either type of specific systemic reaction, that with provoked paroxysm or that with prompt cessation of attacks, constitutes a favorable prognostic sign, especially when supplemented by definite cutaneous reactions. In either type subsequent repeated inoculations on an ascending scale of dosage has usually resulted in improvement. It has thus been found possible to decrease or remove the hypersensitivity to the bacterial causes and sometimes, though not always, to produce an eventual immunity. Two typical cases will be cited in this connection.

The first patient, a female past middle age, had had severe asthma dating

from an attack of lobar pneumonia in 1913. Sputum vaccine containing streptococcus and pneumococcus gave relief in this early phase of her infectious asthma. In 1917, following a recurrence of asthma, she had a cholecystectomy at the Mayo Clinic with good recovery. Her asthma, however, recurred intermittently until 1925. At this time she consulted Dr. A. Fleming at St. Mary's Hospital in London. This worker cultured the stool, found large numbers of streptococci of the viridans type and started vaccine treatment with small doses of this growth. Perfect relief occurred in three weeks and lasted without incident over a period of five years. In 1930 she suffered another mild attack which responded promptly to a similar stool vaccine made by me. This case affords a striking example of the outstanding infectious nature of this group of asthmas.

Another case, a boy of ten, had had asthma every winter from the time of his measles, diphtheria, and pneumonia six years before. Cutaneous tests resulted negatively with the exception of dog, mustard, and flaxseed, all of which gave good reactions. No specific treatment was given for any of these reactors. A high incidence of eosinophiles in the blood and sputum, together with an increased sedimentation velocity, and the hibernial nature of his attacks led to a diagnosis of bacterial asthma. The sputum, which was scanty and of a whitish milky appearance, yielded on culture over 12,000,000 green-producing streptococci per 0.05 cc. Stool culture gave 1,000,000 green-producing streptococci and 55,000 hemolytic streptococci to the helpful. Both

vaccines gave good twenty-four hour reactions on intradermal inoculation and significant immediate reactions were also obtained with the stool vaccine (figure 1, E) and with the protein prepared from the ground up green-producing streptococci. (Figure 1, D). This boy's asthma stopped within a few weeks after vaccine treatment and has not recurred during the whole winter season. In the meantime his weight has increased from 60 to 73¼ pounds during the past six months. Such cases as this represent bacterial asthma with complete desensitization following minute doses of the specific inciting cause.

DISCUSSION

An analysis of the results of specific bacterial therapy is made difficult by the complexity of the bacterial effects in the human organism. These include not only the over-emphasized foreign protein factor but the more significant specific nucleoprotein-carbohydrate antigens which have been established on a scientific basis by the brilliant researches of Avery and Heidelberger,²³ Zinsser, Lancefield and many others. Sabin and Enders have contributed to our knowledge of these specific phenomena and the Dicks and Dochez have added an entirely different hemolytic streptococcus factor, a true toxin which is heat resistant but which incites a specific antitoxin. Any of these components may be present in the bacterial filtrate or capsule or cell body in varying degree, and it is conceivable that any or all of them may be concerned with the manifestations of asthma.

Some attempt has been made to de-

termine the relative importance of the bacterial cell bodies and filtrates. Intradermal tests with these separate bacterial preparations have shown at times a stronger reaction with the one or the other but just as often the two have reacted equally. There have been instances in which the washed organisms have produced a large twenty-four hour areola while the filtrate has scarcely reacted at all. The reverse has sometimes occurred. Such considerations have led me to a routine procedure of using in treatment those bacterial preparations from the sputum or stool or other sources which reacted best, including in most cases both whole organisms and unheated filtrate.

The results have been studied analytically but detailed tabulations have been omitted, because they were considered highly involved and to some extent misleading. The results do, however, lead to certain important generalizations. Table 1 shows that the outcome of treatment in the bacterial and mixed groups has compared favorably with that in the non-bacterial group, due to known foods or dusts. The success obtained is attributed to the selection of cases on the basis of

symptomatic and seasonal considerations, routine blood and sputum examination, and exhaustive culturing followed by administration, in carefully standardized dosage, of those bacterial preparations which have given significant cutaneous reactions. Cases conforming to these requirements and receiving an adequate course of specific treatment have generally had a successful outcome while the others have more often failed of a good result.

The importance of thorough attention to the various food and dust factors has been referred to in a previous report and need not be dwelt on here, nor have the metabolic, endocrine, and other general considerations been overlooked. Space has permitted only the detailed handling of the subject undertaken, namely, the rôle of bacteria.

CONCLUSION

The limited value of non-specific protein shock therapy is admitted. More important, however, in properly selected bacterial cases is the definitely specific desensitization which can be attained by the careful use of autogenous vaccines and filtrates.

REFERENCES

- ¹VAUGHAN, V. C.: The bacterial toxins, Trans. Assoc. Am. Phys., 1901, xvi, 217; A study of bacterial cells, *ibid.*, 1902, xvii, 243; Protein split products, 1913, Lea and Febiger, Philadelphia, p. 17.
- ²DIBLE, J. H.: Recent advances in bacteriology, 1932, P. Blakiston's Son and Co., Philadelphia.
- ³DOCHEZ, A. R., and AVERY, O. T.: Elaboration of specific soluble substance, Jr. Exper. Med., 1917, xxvi, 477.
- ⁴ZINSSER, H., and PARKER, J. T.: Bacterial hypersusceptibility, Jr. Exper. Med., 1923, xxxvii, 275-302.
- ⁵TOENNIESSEN, E.: I. Untersuchungen über die Kapsel (Kummihülle) der pathogenen Bakterien. II. Die chemische Beschaffenheit der Kapsel und ihr dadurch bedingtes Verhalten gegenüber der Fixierung und Färbung, Centralbl. f. Bakteriologie, Abt. 1, Orig., 1921, lxxxv, 225-237, cit. by DIBLE, loc. cit.
- ⁶MUELLER, J. H., and TOMCSIK, J.: Chemical nature of residue antigen prepared from yeast, Jr. Exper. Med., 1924, xl, 343-352.
- ⁷LANCEFIELD, R. C.: Immunological relationship of *Streptococcus viridans* and

- certain of its chemical fractions, serological reactions obtained with antibacterial sera. *Jr. Exper. Med.*, 1925, xlii, 377-395.
- ⁶HITCHCOCK, C. H.: Classification of hemolytic streptococci by precipitin reaction. *Jr. Exper. Med.*, 1924, xl, 445-452.
- ⁷PRZESMYCKI, F.: Specific "residue antigens" of different types of meningococci. *Jr. Infect. Dis.*, 1924, xxxv, 537-539.
- ¹⁰PICK: cited by ZINSSER and PARKER, loc. cit.
- ¹¹SABIN, A. B.: On presence in antipneumococcus serum of type-specific protective antibody not neutralized by homologous specific soluble substance. *Jr. Exper. Med.*, 1931, liii, 93-107.
- ¹²ENDERS, J. F.: Type specific substance distinct from specific carbohydrate in pneumococcus Type I. *Jr. Exper. Med.*, 1930, lii, 235-252.
- ¹³MILLER, J. L.: Typhoid. *Ill. Med. Jr.*, 1916, xxix, 8. Foreign proteins. *Jr. Am. Med. Assoc.*, 1916, lxvi, 1756. The effect of foreign protein therapy in lobar pneumonia. *Jr. Am. Med. Assoc.*, 1920, lxxiv, 1598.
- ¹⁴COCA, A. F., WALZER, M., and THOMMEN, A. A.: Asthma and hay fever, 1931, Charles C. Thomas, Springfield, Ill.
- ¹⁵TOPLEY, W. W. C., and WILSON, G. S.: Principles of bacteriology and immunity. 1929, ii, Wood and Co., New York.
- ¹⁶PILOR, L.: Skin reactions with *Staphylococcus aureus*. *Jr. Allergy*, 1931, iii, 86.
- ¹⁷POTTINGER, F. M.: Similarities and differences in bacterial and non-bacterial allergy. *Jr. Allergy*, 1920, i, 235-244.
- ¹⁸STORR VAN LEEUWEN, A. J., and MAYTUM, C. K.: Bacteriologic study on the etiology of bronchial asthma. *Proc. Staff Meetings, Mayo Clinic*, 1931, vi, 259. (Cited in *Jr. Allergy*, 1931, ii, 516).
- ¹⁹FREUND, cited by VAUGHAN, Protein split products, 1913, Lea and Febiger, Philadelphia and New York.
- ²⁰HARRISON, J.: Spore-producing substance in sputum of patients with bronchial asthma. *Arch. Int. Med.*, 1930, xlv, 641-647.
- ²¹HARRISON, J. K., HARRIS, M. T., and FREUND, M. S.: Production of asthma by tyramine, bronchospastic and arteriospastic substances in blood broth by pure cultures of microorganisms. *Jr. Infect. Dis.*, 1928, xliii, 363-377.
- ²²ARTHUS, M.: Injections répétées de sérum de cheval chez le lapin. *Compt. rend. de la Soc. biol., Par.*, 1903, lv, 817-820. (Cited by VAUGHAN, loc. cit.)
- ²³SHWARTZMAN, G.: Phenomenon of local skin reactivity to bacterial filtrates; passive immunity to reacting factors. *Jr. Exper. Med.* 1931, liv, 1-10; (also see COCA, loc. cit., p. 87).
- ²⁴DICK, G. F., and DICK, G. H.: Experimental scarlet fever. *Jr. Am. Med. Assoc.*, 1923, lxxxi, 1166-1167; Skin test for susceptibility to scarlet fever. *Jr. Am. Med. Assoc.*, 1924, lxxxii, 265-266; Etiology of scarlet fever. *Jr. Am. Med. Assoc.*, 1924, lxxxii, 301-302; Scarlet fever toxin in preventive immunization. *Jr. Am. Med. Assoc.*, 1924, lxxxii, 544-545; Method of recognizing scarlet fever streptococci by means of specific toxin production. *Jr. Am. Med. Assoc.*, 1925, lxxxiv, 802-803.
- ²⁵TOUART, M. D.: Autogenous vaccine skin tests. *Jr. Allergy*, 1929, i, 85-86.
- ²⁶ZINSSER, H.: Significance of bacterial allergy in infectious diseases. *Bull. N.Y. Acad. Med.*, 2nd series, 1928, iv, 351-383.
- ²⁷ZINSSER, H., and TAMIYA, T.: Studies on antigenic substance of bacterial cell. *Jr. Exper. Med.*, 1925, xlii, 311-321.
- ²⁸BENSON, R. L.: A hopeful view of asthma. *Northwest Med.*, 1932, xxxi, 153-160.
- ²⁹THOMAS, W. S.: Asthma, its diagnosis and treatment. Paul B. Hoeber, Inc., New York.
- ³⁰HAIBE, A.: L'asthme bronchique et son traitement. *Ann. Soc. scient. de Bruxelles*, 1930, I, 16-64; also *Rev. belge. de med.*, 1931, iii, 561-612.
- ³¹WEIGHT, A. E.: Studies on immunization. 1909, Constable and Co., London.
- ³²WALKER, L. C.: Treatment of bronchial asthma. *Arch. Int. Med.*, 1919, xxiii, 220; and others.
- ³³AVEBY, O. T., and HEIDELBERGER, M.: Immunological relationships of cell constituents of pneumococcus. *Jr. Exper. Med.*, 1925, xlii, 367-376.

A Method of Evaluation of Results in Hay Fever; Its Application to Certain Modes of Treatment*†

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THE THERAPEUTIC progress in any field necessitates a means at our disposal for measuring therapeutic results. This may imply either an objective method or a good subjective method. In hay fever this is especially desirable because of the natural variations in the symptoms. From time to time various treatments are advocated in hay fever and it becomes necessary to measure their value. Modifications in technic of old accepted forms of treatment must also be evaluated. In addition, the measurement of therapeutic results in hay fever may be of worth also in the study of other factors such as age, complications, climate, etc.

Unfortunately there is no objective method for studying results in hay fever. We must rely entirely on a study of the subjective symptoms. The usual means of studying and reporting hay fever results are very unsatisfactory. The most common method, perhaps, consists of grading results according to the physician's impression of the symptoms for the entire season. Frequently the patient himself is asked to evaluate the season after it is over.

*Read before the Chicago Society of Allergy, January 18, 1932.

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It hardly needs comment to contend that such a method has too many elements of unreliability. Our powers of recollection become diminished in proportion to the time that has elapsed, and this is especially true if the memory is an unpleasant one.

Even the impression gained day by day from studying the immediate or daily effect of treatment is not of great value unless certain factors are taken into consideration. As long ago as the middle of the nineteenth century Blackley¹ noted that there were marked variations in the pollen content of the air during the hay fever season. He also noted that the severity of the symptoms in himself, as well as in other hay fever sufferers, depended chiefly on the concentration of the pollen in the air. This concentration he measured by counting the number of pollens on a unit area of an oiled glass slide exposed to the atmosphere for a unit of time. Duke and Durham² in 1928 emphasized this dependence of severity of symptoms on pollen concentration. They say: "The marked irregularity of the charts (pollen) often accounts for variation in the symptoms displayed by patients from day to day during a given season".

For many years practically all men in the field of allergy have held or ex-

pressed similar views. It remained, however, for Rackemann and Smith,^{3,4} Acquarone and Gay,⁵ and Hopkins⁶ to show graphically this correlation of symptoms and pollen concentration. The symptom curve of Rackemann and Smith is drawn from results of 100 treated patients. The symptoms for each patient are shown by a horizontal line, a light one for mild symptoms and a heavy one for severe symptoms. The symptom curve is obtained by counting the individual lines where they cross the upright date lines, allowing two counts for the heavy lines, and plotting the totals to make the symptom curve. The objection to these curves is that the symptoms are not graded sufficiently, thus not making sufficient distinction between symptoms of varying severity from day to day. No attempt is made to show how treatment of one type or another may influence this symptom curve.

In 1931 Acquarone and Gay⁵ reported a study of the correlation of hay fever incidence in sixty-seven treated patients with that of pollen incidence during 1929. In this study the cases were divided into four groups: tree cases, grass cases, plantain cases, and ragweed cases. The percentage of cases in each group showing symptoms on each day was plotted with the curves made from the pollen counts. On the whole their figures show correlation between pollen counts and the percentage of patients showing symptoms. However, in the ragweed cases, judging from their chart, the correlation was not very constant. The objection to their data and figures is that no differentiation is made between mild and severe hay fever;

"a patient who had symptoms for as short a period as one hour is included in the curve".

Two months after the previous publication, Gay⁷ made a more extensive report of hay fever symptoms in relation to treatment. The patients kept their own records, marking the day "bad" if the symptoms persisted continuously throughout the twenty-four hours; "poor" if there were an hour or two of symptoms during the twenty-four hours; and "good" if there were no symptoms at all. He thus finds, for example, in 1929 that the treated cases averaged a total of 14.4 days of discomfort (8.4 mild symptoms and 6.0 days severe), as compared with a possible 46.2 days in untreated patients. In the ragweed group of that year the treated cases experienced 14.1 days of symptoms, against a possible forty-two days in untreated patients.

Hopkins⁶ also reported a study of the correlation of the pollen with the symptom curve, but she also did not differentiate between grades of severity.

METHOD

The first step is the grading of symptoms. The patient who goes through the season with a little sniffing and no discomfort has an entirely different result from one who has severe symptoms with frequent discomfort. It seemed to me, therefore, in order to arrive at any valuable conclusion as to treatment, etc., there must be a grading of symptoms intermediary between a few sneezes and the most severe form of hay fever. The following plan was adopted and carried out during the 1929 ragweed season. The

symptoms were graded into five classes. Grade 1, "very slight", consisted of only an occasional sneeze; this degree of irritation and sneezing would be ignored by many patients unless their attention was aroused by close inquiry. Grade 2, "mild", consisted of definite hay fever symptoms lasting an hour or two of the twenty-four hours. Grade 3, "moderate", was defined as including the more continuous symptoms, lasting a great part of the twenty-four hours, but not of a very violent nature and without much blocking of the nose. Grade 4, "severe", consisted of blocking of the nose, frequently repeated severe sneezing spasms, very marked rhinitis, or marked eye and throat symptoms; any or all of the above symptoms were present but not constant throughout

the twenty-four hours. Grade 5, "very severe", consisted of the same symptoms as Grade 4, except that they were practically constant throughout the twenty-four hours.

From such daily grading, individual symptom curves may be plotted as seen in chart 4. It may readily be seen that not only is there a tendency for these curves to be correlated with the pollen curve, but each individual curve gives us a graphic idea of the severity of the season for that particular patient.

Chart 1 represents a composite symptom curve obtained by charting and averaging the daily symptoms of a series of patients. Each patient's daily symptoms are represented by a dot. The dots for that day are then averaged, thus giving us an average

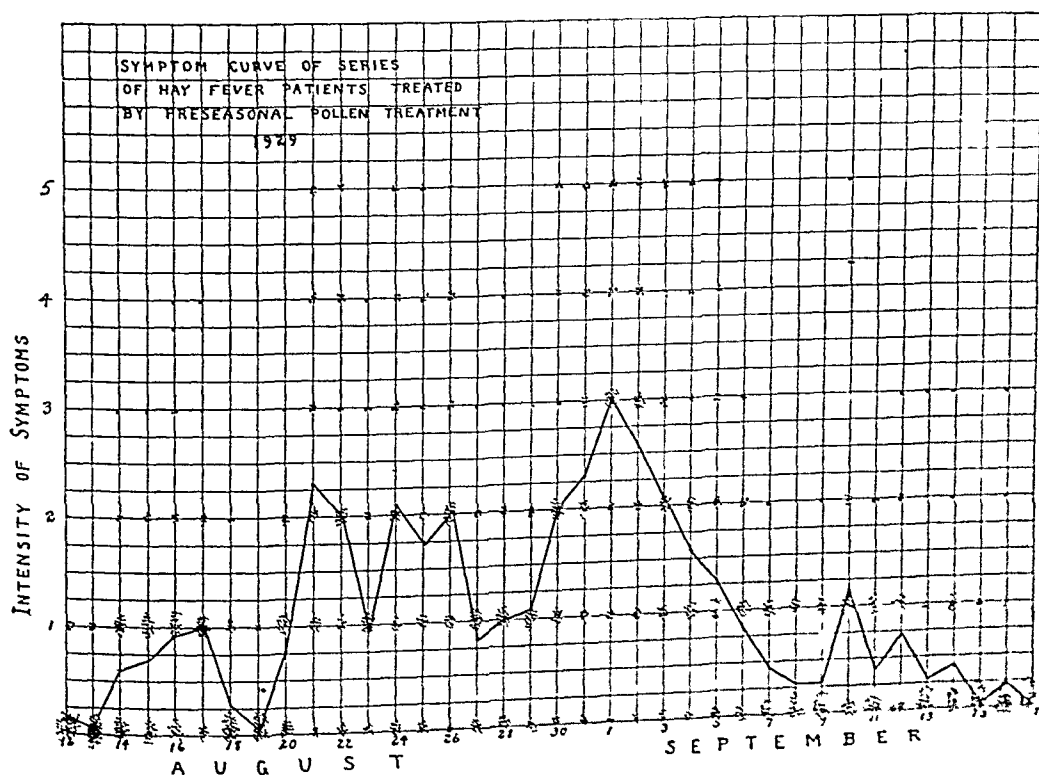
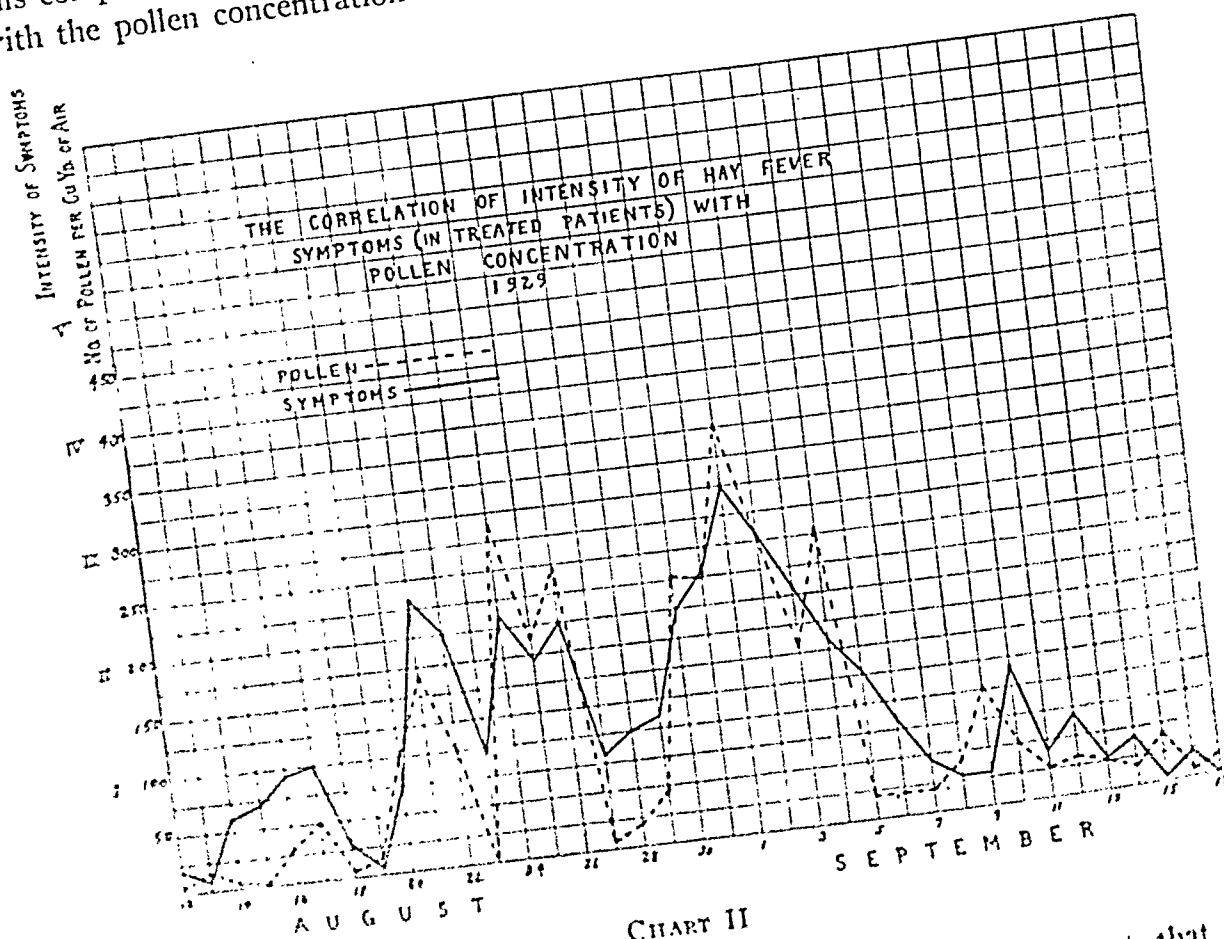


CHART I

daily symptom grade. When all these daily points are connected there is obtained a curve such as outlined in chart 1. The chart is made from a series of fifty ragweed hay fever patients.

Chart 2 shows the correlation of this composite symptom intensity curve with the pollen concentration curve. It

lag between the peaks of the pollen curve and those in the curve of hay fever intensity. Acquarone and Gay⁵ found such a lag of twenty-four to seventy-two hours, possibly because they were charting hay fever incidence rather than intensity of symptoms. At this point it may be observed that on



will be noted that the severity of symptoms follows pretty closely the changes in pollen density. It will also be noticed that in some places on the graph sudden drops in pollen concentration are followed by more gradual changes in the symptom curve. This is probably due to the tendency for the course of pathological changes in the nose even after the pollen has ceased to be present in the air. On the other hand, I fail to find any decided

chart 2 it is also apparent that the average maximum intensity of hay fever symptoms in the treated cases, occurring at the height of the pollen season, is Grade 3, or "moderate", and that during most of the season the average intensity was below Grade 2, or "mild" hay fever.

In chart 3 we have a comparison between the symptom curve of the previously described treated series and the curve of a series of thirty patients

who were untreated or only partially treated. It is evident that in the latter curve there is also a correlation between the intensity of symptoms and the pollen concentration. It is also apparent that the suffering of the average patient among these untreated

content to be thus neglected. It is therefore not unreasonable to think that the symptom curve of a series of absolutely untreated patients would be at a greater height than is depicted in chart 3.

Thus far it may be seen that in any

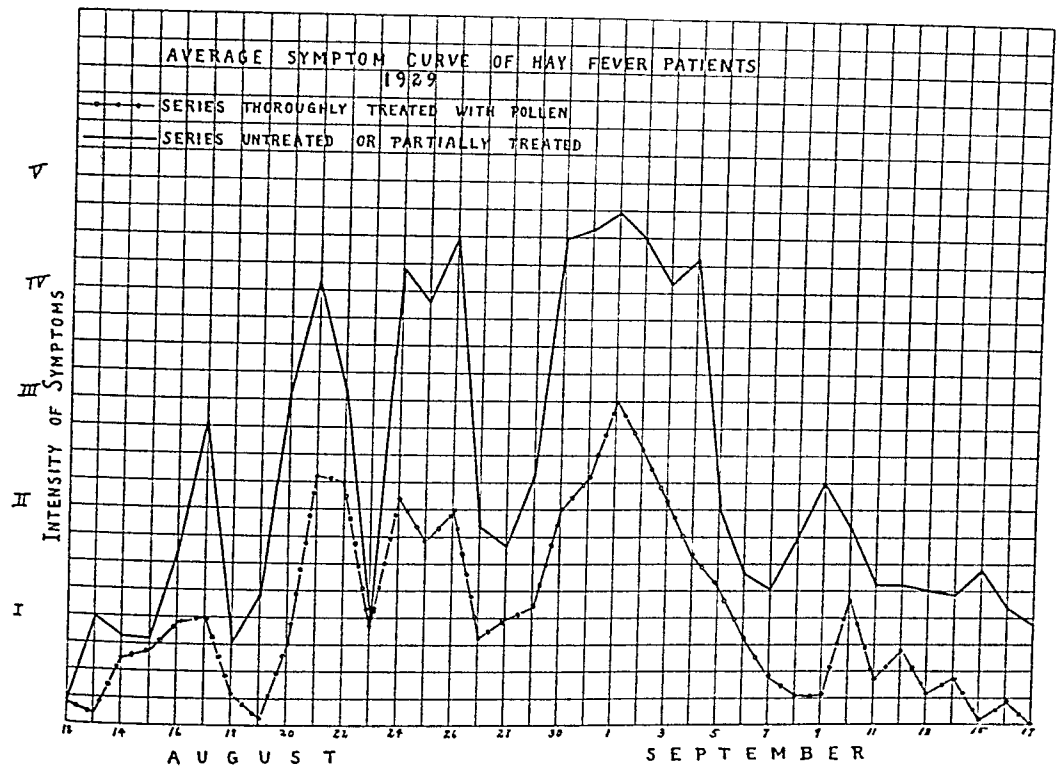


CHART III

cases reaches a greater intensity and is near the maximum for a large part of the season. The "untreated" patients in this series comprise chiefly those who came in at the beginning of the season and had only partial pollen treatment, and those who came in the middle of the season and had only palliative treatment. It is practically impossible to have a series of hay fever patients under observation during an entire season without any treatment whatsoever—the sufferers are not quite

group of hay fever patients the results may be ascertained from a consideration of the average symptom curve or from a consideration of the individual symptom curves. Chart 4 contains five such individual symptom curves, each of which illustrates the usual result under the conditions noted in the chart. It must be emphasized that these individual curves are only examples of their particular series, and that there is considerable variation within the series. However, they serve the

purpose of illustrating the types of curves usually obtained and their interpretation.

The bottom heavy curve shows the typical course of symptoms in a case in which treatment was fairly successful. It will be seen that this patient had many days with no hay fever

The upper three curves represent patients who had considerable hay fever and on whom various methods of treatment were tried during the course of the season. It will be noted in each case that the medication had no effect on the course of the disease. The symptoms continued to be severe

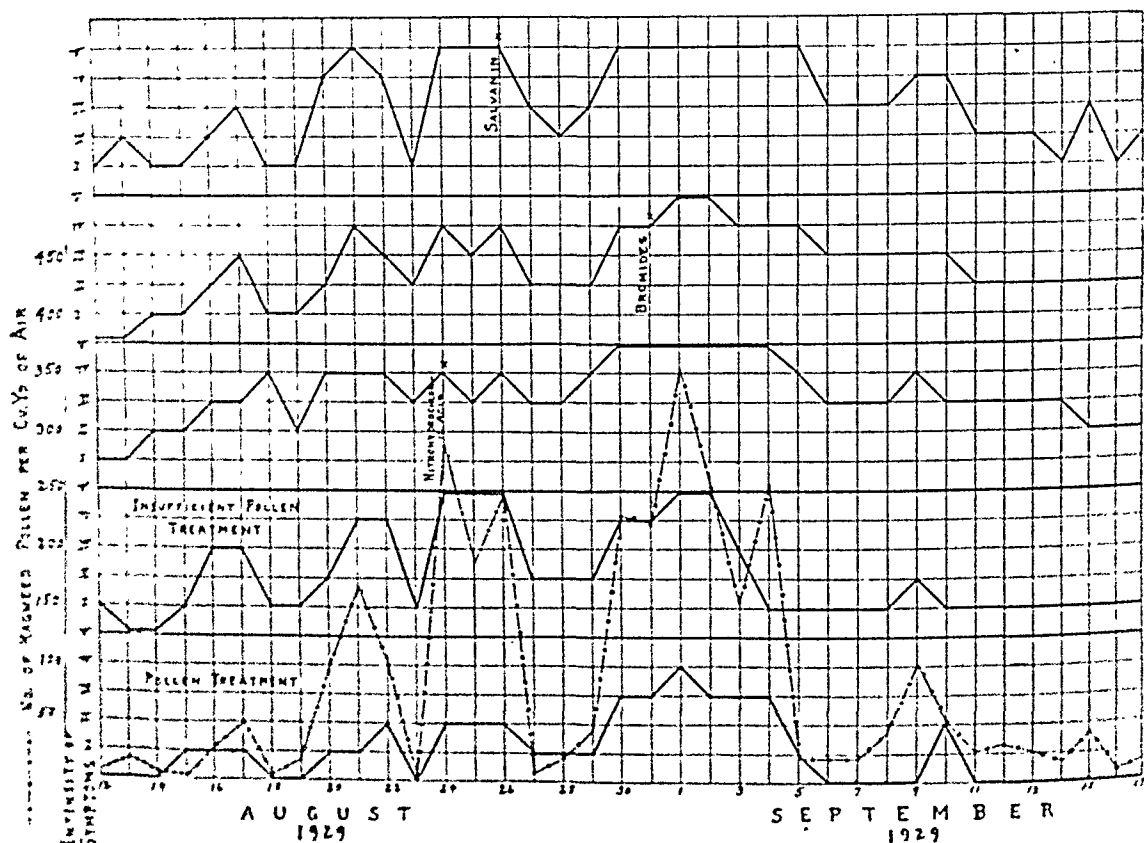


CHART IV

whatsoever, only one day of "severe" symptoms, and the remainder varying from "slight" to "moderate". The curve also shows the variation in the symptoms dependent on the pollen concentration. The curve immediately above it depicts the symptoms of a patient who has had insufficient treatment. The correlation of intensity of symptoms with the pollen curve is not evident, but the curve is at a high level.

and varied with the pollen density in about the same way as might have been expected without treatment. In the top curve it may be seen that the use of "salvamin" begun on August 26th apparently resulted in marked improvement in the patient's symptoms for the next two or three days; but when one consults the pollen curve it is obvious that the fall in the latter was responsible for this improvement. The continued use of this drug did

not prevent a recurrence of severe hay fever when the pollen count rose again.

For comparing results, it is seen that not only must the individual twenty-four hour periods be graded, but the results of the entire season must be evaluated also. The problem here is a little more difficult and there probably can be no absolute measure since the usual suffering of all hay fever patients is not the same and what would be a satisfactory result in an extremely severe case might be a decidedly poor result in another. Of course, it is possible to work out a complicated system for measuring degrees of such results, but it probably would add confusion. I have chosen the following designations: failure, poor season, fair season, good, and excellent. An "excellent" season may be defined as one in which the patient has had no hay fever or very slight symptoms. A "good" season is one in which there has been some hay fever but not enough most of the time to be annoying. A "fair" season is one in which there was definite improvement but in which nevertheless hay fever was present during much of the time. A "poor" season is one in which it can be ascertained that there was some improvement, but not enough actually to relieve the patient from his suffering. It is only slightly removed from a "failure", which latter term speaks for itself.

Thus, after evaluating the results in individual patients and then tabulating the results in a series, we can apply the data made available to finally determine the value of a mode of treatment in hay fever. For example, in a series of sixty-two cases of ragweed hay fever during the same season

treated by adequate pollen therapy 40.5 per cent had "excellent" results, 30.5 per cent "good", 13.2 per cent "fair", 8.9 per cent "poor", and 6.9 per cent "failures".

On the other hand, the nitrohydrochloric acid treatment, which has been so enthusiastically advocated by some,⁸ when evaluated by such a procedure as that discussed above, is shown to be unsatisfactory. For example, in a series of thirty cases during 1929 and 1930 only one had excellent results and possibly two more had fair results. Bromides,⁹ also lauded by some in hay fever, gave no results in a small series of cases. For several years "salvamin", which is the lactone of gallic acidethanolaminochlorhydrate, has been enthusiastically advocated in Germany.¹⁰ A series of eight of our local ragweed cases treated with this drug, when tested out for results by the above discussed methods, showed no effects whatever from the use of this remedy.

In the 1931 ragweed season in a small series of nine hay fever patients the effect of intranasal applications of "cold quartz" radiation (ultraviolet) was tried at the request of the Council of Physical Therapy of the American Medical Association. The previously described method of evaluating results was employed in these cases. Except for slight temporary improvement in a few, lasting one or two hours, this therapeutic procedure failed to produce results.

SUMMARY

1. There is need for a method of evaluating the results in hay fever therapy.
2. Any such method must take into

consideration the natural variability in symptoms due to daily, seasonal, and local variation in pollen concentration. Daily pollen counts are absolutely essential.

3. The method of evaluating the results of any hay fever therapy consists of the following steps:

- (a) The grading of the individual patient's daily symptoms,
- (b) The grading of the patient's entire season,
- (c) The tabulation of the results of

the entire group under investigation,

- (d) The comparison of the total results in such a group as compared with groups treated by usually accepted methods and with untreated cases.

4. The above mentioned method was applied to such proposed remedies as nitrohydrochloric acid, bromides, "salvamin", and intranasal quartz light therapy and showed these to be of no practical usefulness.

REFERENCES

- ¹BLACKLEY, C. H.: Experimental researches on the causes and nature of catarrhus aestivus, (hay fever or hay asthma), 1873, London, Baillière, Tindall and Cox.
- ²DUKE, W. W., and DURHAM, O. C.: Pollen content of air; relationship to symptoms and treatment of hay fever, asthma and eczema, *Jr. Am. Med. Assoc.*, 1928, xc, 1529-1532.
- ³RACHEMANS, F. M., and SMITH, L. B.: Ragweed hay fever: symptoms and pollen concentration compared (1930), *New England Jr. Med.*, 1931, cciv, 711-712.
- ⁴RACHEMANS, F. M., and SMITH, L. B.: Studies in asthma; the plant pollens of New England: their relative importance, *Jr. Allergy*, 1931, ii, 364-371.
- ⁵AQUARONE, P., and GAY, L. N.: A survey of the pollen flora in Baltimore during 1929, *Jr. Allergy*, 1931, ii, 336-355.
- ⁶HOPKINS, M.: Effect of weather variations upon the symptoms of hay fever patients, *Jr. Allergy*, 1931, ii, 145-148.
- ⁷GAY, L. N.: Economic results from the treatment of pollen asthma and hay fever, *Jr. Allergy*, 1931, ii, 456-466.
- ⁸BECKMAN, H.: Nitrohydrochloric acid in treatment of hay fever, *Am. Jr. Med. Sci.*, 1927, clxxiv, 525-529.
- ⁹HAMBURGER, F.: Brom Gegen Heuschnupfen, *Münch. med. Wehnschr.*, 1927, lxxiv, 852.
- ¹⁰HIRSCH, C.: Zur Therapie des Heuschnupfens mit Salvamin Kahlbaum, *Ztschr. f. Laryng. Rhin.*, 1927, xvi, 75-80.

The Patch Test in the Diagnosis of Contact Dermatitis*

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THE greatest problem in the conquest of eczema is the determination of the etiology in a given case. Attempts have been made to differentiate between those cases of eczema due to internal causes and those due to external irritants, the former being designated as eczema and the latter as dermatitis or dermatitis venenata. Such a distinction is often impossible on clinical grounds and should be made only in the presence of positive substantiating proof. The possible exception is a clean-cut case of dermatitis due to poison oak or poison ivy. Here the presence of the eruption in irregular blotches and streaks where branches and leaves have rubbed against the exposed parts of the body is suggestive. Also the usual violent type of vesiculation and edema, especially if coupled with a history of exposure within twenty-four to forty-eight hours prior to the onset of the eruption, is usually sufficient to establish a diagnosis.

Fundamentally there is no difference either histologically or in most cases clinically between an eczema of inter-

nal or external origin. The essential point is not a matter of labelling a given eruption eczema or dermatitis venenata but of proving the etiology and of incorporating it in the diagnosis. No one could quarrel with a diagnosis of eczema (food allergy) or eczema (primrose), although if one preferred to use the designation dermatitis venenata (primrose) the diagnosis would be equally valid.

Sometimes the location of an eczematous eruption will suggest an external etiology, but too much dependence should not be placed on such evidence as it will often prove misleading. For instance, arsenical dermatitis due to intravenous therapy or to poisoning from contaminated food, may first manifest itself on the exposed parts of the body and may for a long time show a predilection for these areas. In such cases exposure to the sun aggravates the eruption, but it would be telling only half of the truth to say that such a case of eczema was due to idiosyncrasy to the sun's rays, and if the investigation went no further the patient certainly would not be cured.

Such misleading clues are frequently encountered. It becomes all the more important, therefore, to prove the relationship between a given eczematous

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eruption and a suspected irritant. The so-called scratch test, in which a small amount of an antigen, usually food, pollen, or hair protein, is mixed with tenth normal sodium hydroxide and applied to the skin by means of a small scarification on the arm, is useful, especially in cases of food sensitization and in some instances of eczema due to contact with animal hair or pollen. Instances have been encountered, however, in which a scratch test with a pollen was negative while the patch test was strongly positive.

The patch test, therefore, is particularly useful in detecting those substances, protein and non-protein, which by external contact produce an eczematous reaction. The test has been used for some years in Europe, but it is only during the past three or four years that it has been employed to any extent in this country.

The first essential is a detailed history with especial reference to contact with possible irritants in the patient's occupation, hobbies, surroundings, the local use of medication or cosmetics, etc. There are two important points in such a history which may be confusing. The fact that a patient has handled a certain substance for many years without irritation is no proof that this substance may not be the cause of the present eruption. The skin resistance to a given substance may break down or, to put it in another way, the skin may become hypersensitive after prolonged contact, so that an attack of eczema ensues after each subsequent exposure. The second confusing point is the fact that the eruption may be caused by contact with a given irritant at one point, for

example on the arm, and may spread over large areas of the body. It is also important to remember that any substance, no matter how benign it may appear, may be the cause of the eruption in question.

When a careful history has narrowed down the list of probabilities, the test is applied in the following manner. Every effort should be made to simulate the original condition under which the irritation took place. If the substance is a chemical it should be applied in approximately the same dilution to which the patient has been previously exposed. Leaves of plants and shrubs should be as fresh as possible. Dry powders may be moistened slightly with water. The substance to be tested is placed on a small square of cotton about the size of a postage stamp which is then applied to the flexor surface of the forearm, or other suitable area, and covered with a square of some impervious material such as cellophane, which should be about four times as large as the test area. This external covering is then held firmly in place by wide strips of adhesive tape. The space on all sides between the edges of the central cotton square and the edges of the cellophane is sufficient to prevent the adhesive tape from coming too close to the test area. Otherwise the mild temporary irritation which usually results from the adhesive tape might interfere with an accurate interpretation of the reaction. The patch test is allowed to remain undisturbed for twenty-four hours unless discomfort from irritation justifies its removal before this time. A positive reaction is characterized by a sharply defined square of

redness corresponding in size and shape to the central test area. Papules and vesicles are also usually present, corresponding to the appearance of the original eruption. Evidences of the reaction can usually be noted for three or four days or longer after the test is applied. In rare instances the reaction may not develop for forty-eight hours after the test is applied.

The test is simple, inexpensive, and closely simulates the natural conditions under which the dermatitis developed. It is usually very accurate. A few cases have been reported in which only certain areas of the skin were hypersensitive so that in the case of a dermatitis of the face, a patch test on the arm was negative while one performed on the face after the eruption had subsided was strongly positive. Such instances are probably uncommon, but the possibility should be borne in mind.

CLINICAL REVIEW

During the past two years, we have made patch tests on forty-seven private patients; of these twenty-four have been positive, twenty-one negative, and two of doubtful interpretation. The value of the test lies not only in the positive reactions which definitely establish the etiology, but also in the negative results which exclude certain suspected substances. In nine of the twenty-one patients who did not react to the patch test, subsequent investigations along other lines revealed other causative agents such as fungi, yeast, arsenic poisoning, food and pollen allergy, and infection with *demodex folliculorum*.

The following is a list of the substances which have given a strongly

positive reaction in the twenty-four cases in this series.

PLANTS:

Primrose, lantana, geum, wigandia, summer grass, wild mustard.

COSMETICS:

"Dew" (for hyperidrosis), henna, (red and bronze), Inecto (hair dye). These positive tests were all obtained on the same patient.

DRUGS:

Ammoniated mercury ointment (two per cent), butesin picrate ointment (three cases), adhesive tape (B & B), procaine (two cases), oil of eucalyptus, ephedrine sulfate solution, ephedrine butesin (Abbott 1755).

INDUSTRIAL IRRITANTS, ETC.

"Calcium", a liquid containing essentially 40 per cent calcium chloride, used in hardening cement.

Union cleaning solvent.

Gas gauge fluid (a red liquid used in the gasoline gauge on the dashboard of certain automobiles).

Ground rubber and cement.

Many other substances have been reported which have caused eczematous eruptions by local contact, and doubtless many others hitherto unreported will in the future be incriminated by means of patch tests. Cases of poison oak dermatitis are usually so characteristic that we have made no effort to control such a diagnosis by the patch test.

A few of the cases in this series are sufficiently interesting to justify reporting them briefly in order to illustrate certain points. The danger of placing too much reliance on circumstantial evidence and on the clinical appearance is well demonstrated in the cases of two dentists who were seen within a few days of each other, both of whom presented eczematous eruptions on the hands.

CASE I

Dr. D.S.B. had had an eruption of the hands and fingers at intervals for one and a half years. He had used procaine for two and a half years before the onset of the eruption. For a period of eleven months since the onset of the eruption he had remained away from his office and during this time the hands had remained well. The eruption had reappeared four or five days after his resumed use of procaine. A second vacation of six weeks resulted in a disappearance of the eruption which, however, recurred

within a few days after his return to work. A detailed general history did not reveal any abnormalities. The eruption involved the fingers and consisted of a scaling condition which extended beneath several of the nails. (Figure 1) The right index finger presented a few deep-seated vesicles. Microscopic examination of scales and vesicles was negative for fungi. "Mosaic" forms were found on microscopic examination of a few insignificant scales from between the toes. A patch test of procaine solution was still strongly positive four days (figure 2)



FIG. 1. Procaine dermatitis in a dentist. (Case I)

after it was applied and had not entirely disappeared four weeks later. The reaction was slow in developing, not reaching its height for at least forty-eight hours after the test was applied. Eight months later the patient injected two minims of procaine into his arm. An area of redness developed within twenty-four hours; the anesthesia lasted for three and a half days following which the entire area sloughed out. When the same amount was injected into the arm of his

associate, the anesthesia lasted only three and a half hours and there were no evidences of irritation.

CASE II

Three days after Dr. B. had made his last visit, Dr. L.W., also a dentist, consulted us about an eruption of two weeks' duration on the hands. There were areas of redness and scaling with a tendency to fissuring on the fingers and backs of the hands and an especially irritated area on the left



FIG. 2. Positive patch test with procaine. (Case I)

index finger. (Figure 3) There was some scaling between several toes. A patch test with procaine was negative after twenty-four hours and showed no sign of reaction during the next five days. Microscopic examination of scales from the hands, macerated in 40 per cent potassium hydroxide,

butesin picrate have been reported in the dermatological literature and three such cases occurred in this small series of twenty-four patients. One of these cases illustrates not only the type of the eruption but also the spreading of the rash to areas apparently not originally in contact with the irritant.

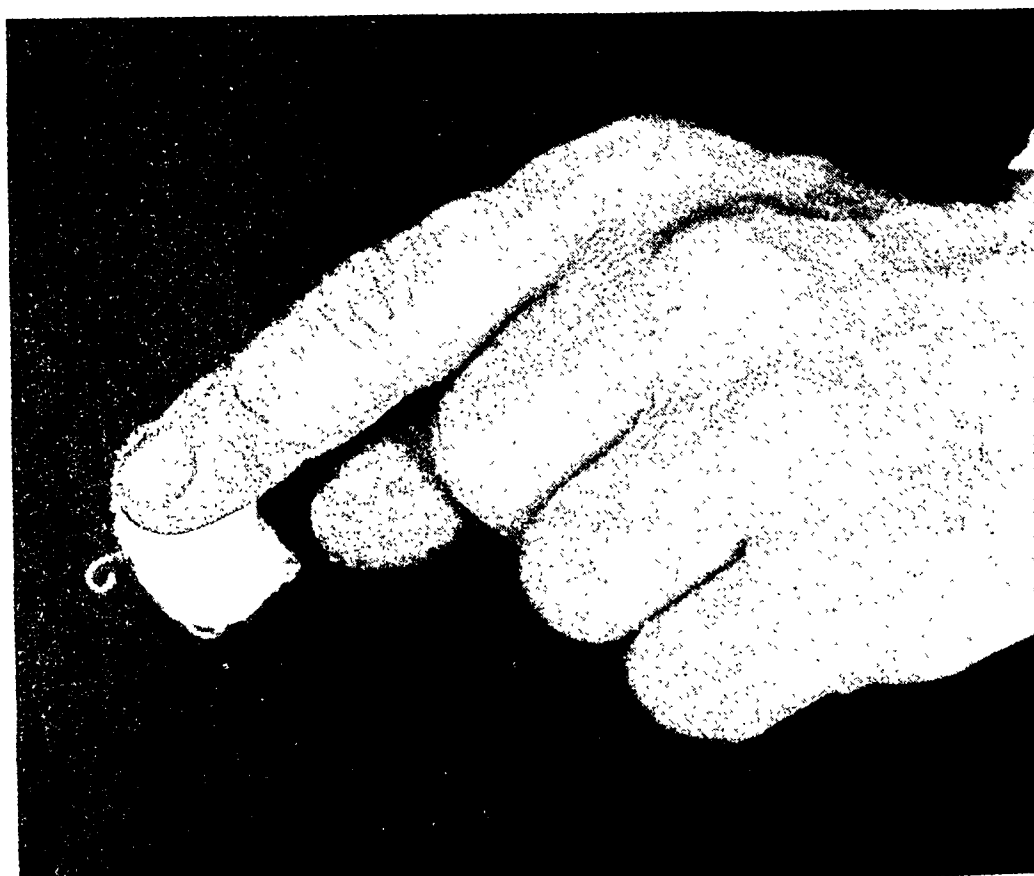


FIG. 3. Epidermophytosis involving index finger and thumb. Negative patch test with procaine (patient was a dentist). Positive microscopic examination for spores. (Case II)

showed typical chains of spores. "Mosaic" forms were found in scales from the feet. A culture from the toes was positive for monilia. No culture was made from the hand.

These two cases afford an interesting problem in differential diagnosis. The clinical appearance in both cases was similar and the exposure to procaine was suggestive of a contact dermatitis. The positive patch test and the negative microscopic findings in the one case, and the negative patch test and positive microscopic findings in the other established a clean-cut diagnosis in both.

Many instances of hypersensitiveness to

CASE III

J.M., a boy about twelve years old, injured his left elbow which was immobilized with adhesive strapping. A few weeks later a blister developed under the adhesive. The adhesive was removed and butesin picrate ointment applied. Considerable irritation resulted and several other remedies were tried, but were not successful in controlling the eruption. When he reported for observation the eruption had been present for about one month and had involved extensive areas of the body. The left arm was red, edematous, oozing, and crusted. The face, neck, chest,



FIG. 4. Dermatitis venenata due to butesin picrate. Note marked inflammatory reaction at site of application (left arm) and also involvement of face, neck, and anterior chest, e.g., areas not having had contact with the original irritant. A positive patch test was obtained. (Case III)

and other arm presented a more diffuse erythematous, blotchy appearance. (Figure 4) This diffuse eruption had been present only a week. Under the use of mildly astringent and antiseptic wet dressings the eruption gradually subsided. Patch tests were made with butesin picrate ointment and with adhesive tape. The adhesive tape did not irritate but the test with butesin picrate was strongly positive.

CASE IV

Mr. H.C. represents another instance of irritation from butesin picrate ointment, showing also a delayed reaction from the test. Two weeks before coming in, he was badly sunburned while driving in an open car with the top down. Two days later he applied butesin picrate ointment which seemed to irritate. The "sunburn" seemed to last an unusually long time but was gradual-



FIG. 5. Dermatitis venenata due to butesin picrate ointment. (Case IV)

ly subsiding, when the night before coming in he again applied butesin picrate ointment. This resulted in a severe flaring-up of the eruption. Examination revealed an eruption limited to the face and neck, and especially pronounced on the front of the cheeks and nose, which were diffusely red, covered with vesicles, yellow crusts, and serous exudation. (Figure 5) A patch test with butesin picrate ointment was negative on removal twenty-four hours later but began to develop redness and vesiculation within a few more hours. Two days after it had been removed the test area was still violently inflamed.

Butesin picrate contains two substances, both of which have been known to cause irritation. Picric acid is a tri-nitro-phenol and butesin is butyl-para-amino-benzoate.

Henna, a vegetable dye, is usually regarded as an innocuous coloring preparation for the hair. In fact some textbooks state definitely that it is non-irritating. Inecto, a proprietary dye, also claims to be free from irritating properties. That such dogmatic statements are unjustifiable is shown by the following case.

CASE V

Mrs. J.M., a beauty shop operator, had been having an eruption of the hands and arms at intervals for two months. The present eruption had been in evidence two days. The eruption was limited to the hands and arms, extending for a short distance above the cubital spaces. The entire involved areas were red, edematous, covered with exudate and crusts and fissured in places. The greatest involvement was on the flexor surfaces. (Figure 6) There was a mild erythematous-vesicular eruption on the face and chin. Patch tests were made with eleven preparations used in hair-dressing. Inecto, red henna, and bronze henna gave strongly positive reactions after twenty-four hours, the greatest reaction being caused by red henna. Five days after the eruption had subsided, a new outbreak began on the fingers, spreading to the hands, forearms and several days later to the anterior aspects of the thighs just above the knees where she had rested her arms. This recurrence followed shampooing a woman's hair which had previously been dyed with Inecto.

Each case history is a veritable detective story, at times taxing the powers of observation of both physician and patient. It is obviously impractica-

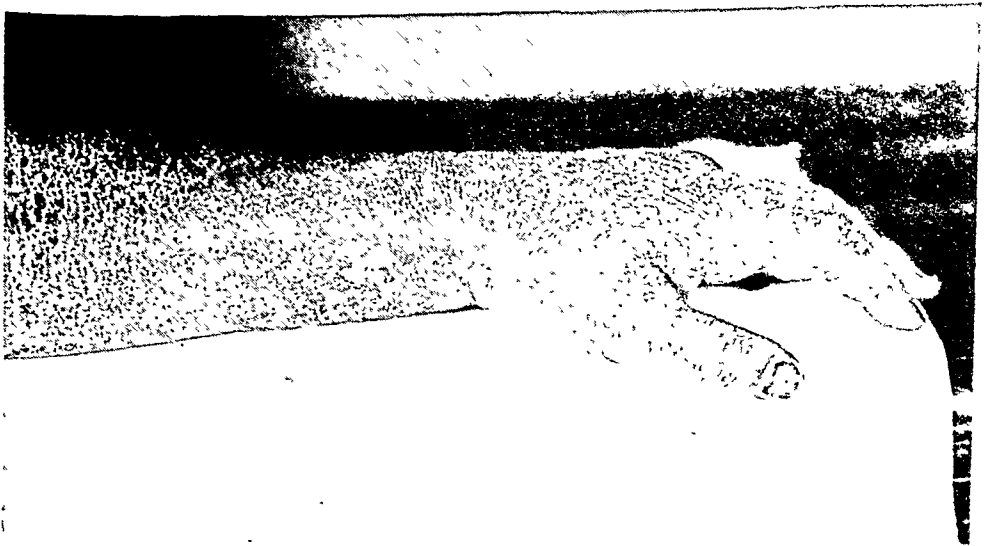


FIG. 6. Marked dermatitis venenata in a beauty shop operator who was shown to be sensitive to Inecto, red henna, and bronze henna by means of patch tests.

ble to test all of the substances with which a patient may come in contact. It is a serious error, however, to disregard any substance simply because it has not been reported previously as a cause of dermatitis. Assisted by a careful history and an intelligent clinical examination, the patch test is invaluable in determining the etiology of many eczematoid eruptions. It is just as much the duty of the physician to prevent recurrences of a disease as it is to treat the present attack. In the case of the eczematoid

eruptions as with most other diseases, an understanding of the etiology is the indispensable factor in preventing such recurrences.

SUMMARY

1. The advantages of the patch test in determining the etiology of certain cases of dermatitis are mentioned, together with a description of the method of applying the test.

2. Twenty-four cases of eczematoid dermatitis are reported, some of them in detail, in which the etiology was established by means of the patch test.

REFERENCES

- ¹JADASSOHN: Zur Kenntnis der medikamentösen Dermatosen, *Jahrb. d. schles. Gesellsch. f. Vaterl. Cult.*, 1896, Bresl., 1897, lxxiv, 1 abt., Med. Sect., 40-44.
- ²MARKLEY, A. J.: Anaphylactoid dermatitis due to direct contact with animal epidermal structures, *Arch. Dermat. and Syph.*, 1920, ii, 722-724.
- ³HIGHMAN, W. J.: The pathogenesis of dermatitis including eczema. A case of English ivy poisoning, *Arch. Dermat. and Syph.*, 1924, ix, 344-354.
- ⁴HIGHMAN, W. J.: Eczema and dermatitis, *Arch. Dermat. and Syph.*, 1925, xi, 303-330.
- ⁵BLOCH, B.: The rôle of idiosyncrasy and allergy in dermatology, *Arch. Dermat. and Syph.*, 1929, xix, 175-197.
- ⁶SULZBERGER, M. B., and WISE, F.: Ragweed dermatitis with sensitization and desensitization phenomena; report of a case, *Jr. Am. Med. Assoc.*, 1930, xciv, 93-95.
- ⁷SULZBERGER, M. B., and LEWIS, G. M.: Trichophytin hypersensitiveness demonstrated by contact tests; preliminary report, *Arch. Dermat. and Syph.*, 1930, xxii, 410-413.
- ⁸RAMIREZ, M. A., and ELLER, J. J.: Intra-dermal, scratch, indirect and contact tests in dermatology; comparative study, *Jr. Am. Med. Assoc.*, 1930, xcv, 1080-1083.
- ⁹BROWN, A., MILFORD, E. L., and COCA, A. F.: Studies in contact dermatitis; nature and etiology of pollen dermatitis, *Jr. Allergy*, 1931, ii, 301-309.

Some Observations Concerning a Possible Insulin-Inhibiting Substance in Urine*†

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RECENT investigations have pointed to the existence in the blood of a substance which is capable of inhibiting the activity of insulin. Karelitz, Cohen, and Leader,¹ as the outcome of an attempt to discover the cause of insulin resistance in a patient with diabetes mellitus, observed that the blood of diabetics, and to a lesser extent that of normal persons, apparently possessed something which was antagonistic in its action to insulin. While this inhibiting property was demonstrated by blood plasma, it was exhibited to a more marked degree by laked red blood cells. Their data were elicited by studying the blood sugar of rabbits before and after the subcutaneous injection into these animals of mixtures of blood and insulin.

The practical significance of these observations is as yet undetermined. While they may not warrant the elucidation of any new theory regarding the pathogenesis of diabetes, they at least provide grounds for speculation. The cause or causes underlying the principal manifestation of diabetes, namely hyperglycemia, is by no means thoroughly understood. While it is generally agreed that this disease is the result of a deficiency of active insulin in the organism, the known facts do not conform with the view that in every case there must be a deficiency in the production or output of this hormone by the islet tissue of the pancreas. In fact, Warren² refers to an "intriguing group of cases without definite anatomical change in the pancreas or other organs". In his series of 300 diabetic autopsies "the pancreas was available for detailed histological study in 259. Of these, 69 were normal so far as could be determined". Cases of clinical diabetes without a pathological background have baffled the pathologist and mystified the clinician. Surely such cases invite an explanation and anything which might throw light upon this dark corner of medicine should be welcome. Unfortunately, short of a postmortem examination, there is no means of distinguishing those cases which possess anatomical changes from those which do not. According to existing knowledge, there is as much, if not more, justification for explaining the latter type of case on the grounds of insulin inhibition as in any other way.

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Accepting the feasibility of neutralization of insulin within the blood stream, the exact nature of the substance or substances responsible for the phenomenon is unknown. Karelitz et al,¹ as a result of their experiments, concluded that the inhibiting agent was probably enzyme-like in character and suggested that it might be trypsin. Their assumption was based partly upon the fact that trypsin is known to inactivate insulin and partly upon their own observations that the insulin-inhibiting property of blood could be diminished or destroyed by heating the blood preliminary to the addition of the insulin. If their conjecture be true, it must be assumed that trypsin is present in the blood of normal persons and that its concentration is increased in diabetes thus accounting for the greater inhibitory effect of diabetic blood. Mauriac and Aubertin³ had reported previously the antagonistic action of diabetic and normal blood plasma and cells upon insulin action. They believed that a so-called anti-insulin substance resided within the red blood cells and that it diffused from there to the plasma. They also advanced the idea that possibly in some cases of diabetes the permeability of the cells was increased thus allowing more anti-insulin to enter the plasma. Epstein and Rosenthal,⁴ as an outcome of some experimental observations on animals, proposed the "trypsin theory" as a possible explanation of certain clinical cases of hyperglycemia and glycosuria. The gist of their contention is that under certain conditions changes in the permeability of the endothelium of the blood capillaries of the pancreas occur,

as a result of which the secretory products of the acini, particularly trypsin, gain access to the blood stream. Since the islets and acini of the pancreas possess a common blood supply, opportunity is provided for immediate contact of internal and external pancreatic secretions, hence neutralization of insulin by trypsin. The same investigators demonstrated also that when trypsin entered the portal blood stream glycogenolysis in the liver resulted.

PRESENT INVESTIGATION

Realization of the fact that further work along these lines is necessary before any practical application can be made of the above-mentioned contributions led to the idea that some information might be gained from investigating the urine in a manner similar to that which has been used by others in studying the blood, to decide whether or not the insulin-inhibiting factor passes from the blood stream into the urine. If such excretion does occur, provision thus might be afforded for learning something of its nature and properties when separated in a natural way from the proteins of the plasma.

If the blood does contain some soluble substance, enzymic or otherwise, capable of influencing insulin in the manner indicated, it is reasonable to surmise that its presence should be manifest in the urine. Therefore, the first requisite in pursuit of the problem would be to ascertain whether or not urine does show any evidence of insulin-inhibiting effect; if so, whether this is more pronounced with the urine of diabetics than with that of non-diabetics, and finally to attempt to gain

some information regarding the nature of this phenomenon.

At the outset, the undertaking is beset with difficulties and the opportunities for fallacious results and conclusions are numerous. However, the findings thus far have proved sufficiently enlightening to warrant the presentation of this preliminary report, the details of which follow.

METHODS OF INVESTIGATION

One c.c. of a solution containing one unit of insulin per c.c. was added to 5 c.c. of urine. After incubating at 37°C. for thirty minutes the mixture was injected subcutaneously into the flank of a rabbit which had received no food during the preceding twelve hours. As control tests, 5 c.c. of normal saline solution were used in place of the urine. Samples of blood for estimations of the blood sugar were obtained from the marginal vein of the rabbit's ear immediately before and at intervals of one, two, and three hours after the injection. The method used for estimating the blood sugar was that described by Pickard and Pierce⁵ employing 0.1 c.c. of blood.

One complete experiment consisted of one or more tests with saline and insulin to ascertain the normal response of the rabbit to one unit of insulin followed by a test using one unit of insulin with unheated urine from a patient with diabetes; another, using one unit of insulin with a sample of the same urine after it had been heated; and still another test, using one unit of insulin with urine from a non-diabetic hospital patient who was not acutely ill, or from a normal person. During the conduct of an experi-

ment as outlined above the same animal was used throughout. A different rabbit was used for each similar set of tests.

In the majority of cases, the urine employed was that excreted during the early part of the day before breakfast and in the case of diabetics before the morning dose of insulin had been administered. Instructions were given for the individual to empty the bladder immediately upon awakening in the morning. This urine was discarded so far as the purpose of the present investigation was concerned. About one and one-half hours later, the specimen for the test was obtained by voiding or, as in the case of adult female patients, by catheterization. By using the morning urine after a preliminary emptying of the bladder it was hoped to avoid the effect of any excreted insulin which might have escaped from the circulating blood during the night in insulin-treated diabetics. Also, by having the specimens secured at that time it was thought that a more constant and comparable concentration of the urine might be obtained. The series of cases under consideration does not include any patients with infections since it is known that infection in some way depresses the effectiveness of insulin. Routine examinations were carried out on all specimens of urine before use and any that were found to contain protein, pus, or blood cells were discarded. The presence of sugar or acetone in the specimens appeared not to influence the results as evidenced by control tests with solutions containing amounts of these substances comparable with those in the urine samples. For the purpose of non-dia-

betic controls, specimens from persons of similar sex and age as the individual diabetics were employed.

In order to test the effect of temperature upon the urine with regard to its insulin-inhibiting property, a portion of each sample of diabetic urine was heated in a water-bath. In some instances, it was subjected to a temperature of from 55° to 60°C. for from three to eight hours. In others, it was placed in boiling water for from five to twenty minutes. After the heating and subsequent cooling, any depletion in volume was made up by the addition of distilled water. The specimen was then kept at ice-box temperature until the next morning when the test with insulin was carried out in exactly the same manner as with the unheated urine.

In consideration of the importance of reaction conditions on the activity of insulin, the reaction of each sample of urine was adjusted to pH 6.4 before the addition of the insulin. This figure happened to be the reaction of the saline solution used throughout these experiments and for that reason was adopted as the standard.

In view of the relative inconstancy of the blood sugar concentrations of fasting rabbits and of their response to one unit of insulin, the method of expressing the results for purposes of comparison was that employed by Culhane⁶ in the assay of insulin. According to this method, the blood sugar concentrations at one, two, and three hours were added together and the sum of these divided by three to obtain the average level of the blood sugar following the injection. The resulting figure was then subtracted from that

representing the blood sugar immediately preceding the injection. The difference was finally expressed in percentage of the original blood sugar finding. This gives what is referred to as the percentage fall of the blood sugar.

RESULTS

The basis of this report consists of the results obtained in twenty-five complete experiments as referred to above; each consisted of four parts, making in all 100 individual observa-

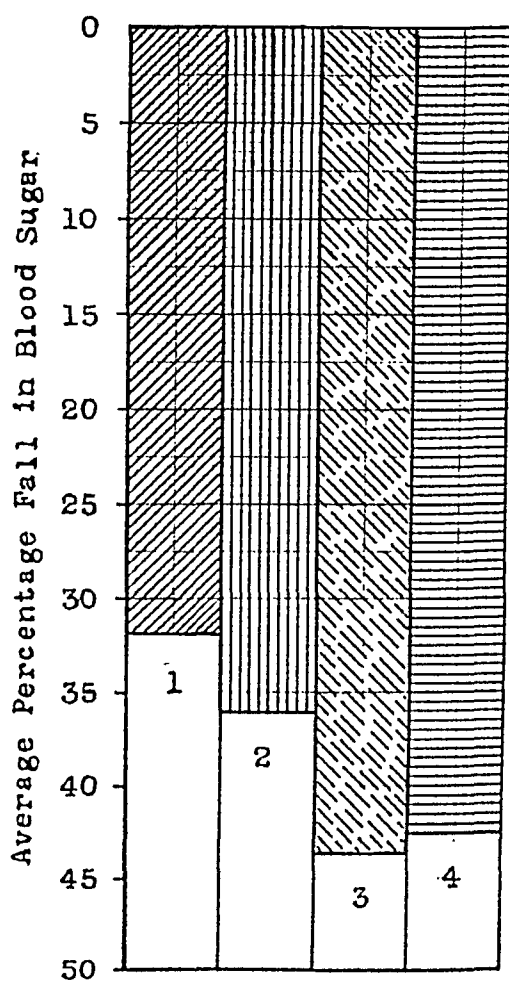


FIG. 1. Comparison of the average percentage fall in the blood sugar of rabbits following the injection of one unit of insulin and 5 c.c. of (1) unheated diabetic urine, (2) non-diabetic urine, (3) heated diabetic urine and (4) normal saline solution.

tions. Whereas no indisputable conclusions can be drawn from such a relatively small number of tests, some points of interest evolve from an analysis of the findings. As might be expected in an investigation of this kind, some discrepancies were encountered but comparison of the various parts of the experiments considered as groups yields some rather definite results.

By assembling all the data into four groups and comparing the average percentage fall of blood sugar thus obtained with unheated diabetic urine, heated diabetic urine, non-diabetic urine and saline as depicted in figure 1, it is seen that diabetic urine causes the greatest amount of insulin inhibition, non-diabetic rather less, and heated diabetic urine none at all as compared with the saline controls. Consideration of the series as a whole suggests at least some differences in the effects of the various test substances upon insulin

action. Further comparisons reveal the nature of the tendencies. Reference to table 1 shows that the fall in blood sugar following the injection of unheated diabetic urine and insulin was less than that obtained with similar amounts of normal saline and insulin in twenty out of the twenty-five experiments (80 per cent). The fall was greater in four cases (16 per cent) and showed no difference in one case (4 per cent). In every experiment the decline in the blood sugar was greater with the diabetic urines which had been heated than with the unheated portions of the same samples, indicating more marked insulin effect in the former or, in other words, destruction of the insulin-inhibiting factor by heat. The urine of non-diabetic hospital patients and of normal persons was capable apparently of causing at least slight inactivation of insulin. In eighteen cases (72 per cent) the fall in blood sugar was less with non-diabetic

TABLE I

Observation	Number of cases	Per cent
Fall in blood sugar with unheated diabetic urine and insulin <i>less</i> than with normal saline and insulin	20	80
Fall in blood sugar with unheated diabetic urine and insulin <i>greater</i> than with normal saline and insulin	4	16
Fall in blood sugar with unheated diabetic urine and insulin the <i>same</i> as with normal saline and insulin	1	4
Fall in blood sugar with unheated diabetic urine and insulin <i>less</i> than with heated diabetic urine and insulin	25	100
Fall in blood sugar with non-diabetic urine and insulin <i>less</i> than with normal saline and insulin	18	72
Fall in blood sugar with non-diabetic urine and insulin <i>greater</i> than with normal saline and insulin	6	24
Fall in blood sugar with non-diabetic urine and insulin the <i>same</i> as with normal saline and insulin	1	4
Fall in blood sugar with unheated diabetic urine and insulin <i>less</i> than with non-diabetic urine and insulin	15	60
Fall in blood sugar with unheated diabetic urine and insulin <i>greater</i> than with non-diabetic urine and insulin	9	36
Fall in blood sugar with unheated diabetic urine and insulin the <i>same</i> as with non-diabetic urine and insulin	1	4

urine than with saline. It was greater in six cases (24 per cent) and showed no change in one (4 per cent). The fall was less with diabetic urine than with non-diabetic urine in only fifteen instances (60 per cent). It was greater in nine cases (36 per cent) and the same in one (4 per cent).

With regard to the degree of severity of the diabetes in relation to inhibition of insulin by urine, there appeared to be some difference, although not pronounced, between the effect of urine from cases labelled severe and those classified as mild. Urine from the severe cases did tend to exhibit more marked inhibitory effect upon insulin than did that from the so-called mild cases.

It would appear from the data presented above that urine probably does contain a thermolabile substance which has an antagonistic influence upon insulin activity although its existence is not proved. While this substance appears to exist in the urine of non-diabetics it seems to be present in slightly greater concentration in the urine of diabetics. Since it has been shown by others that a thermolabile insulin-inhibiting agent is present apparently in blood plasma^{1,3} it would seem reasonable to assume that the substance in urine which is responsible for somewhat similar effects is the same as that which is present in the blood.

DISCUSSION

The only evidence in favor of an enzyme-like character of this special urinary constituent is its behavior toward heat. A more detailed study of its properties is in progress. While

it may be trypsin or trypsinogen no unmodified claim is made to that effect. As a matter of fact, the balance of evidence is rather opposed to such a view. Trypsin is a powerful proteolytic enzyme and normal blood contains probably only a very small amount of it in the active state owing to the presence of anti-trypsin. Of the pancreatic enzymes, diastase is found in urine normally but trypsin and lipase are believed to appear there only under special conditions. Trypsin is present chiefly as trypsinogen, especially abundant after a meat diet.⁷ Wago⁸ found that following the intravenous injection of pancreatin into rabbits the proteolytic pancreatic ferment was excreted rapidly and abundantly into the urine. Thus it is seen that it is possible for trypsin or trypsinogen to gain access to the urine under certain conditions. Its concentration there, apart from the factors which influence the concentration of the urinary constituents in general, might depend upon an increased trypsin content of the blood or diminished production of anti-trypsin. In this regard it should be mentioned that Iacono,⁹ in investigating the external secretions of the pancreas in the blood of diabetics, found that the trypsin content did not show any appreciable change over that of non-diabetics.

There are still other avenues of speculation. For example, Loewi¹⁰ has described a hormone-like substance called glycemin believed to be formed in the liver which interferes with the utilization of glucose by the tissue cells. The existence of this substance is, however, problematical.¹¹ Then there is the possibility of the absence or

deficiency of some complement or coferment which may be necessary for insulin to exert its full effect. But as pointed out by Karelitz and his co-workers,¹ acceptance of this conception implies inadequacy of these factors in normal blood in vitro and still more marked inefficiency in diabetics.

It has been suggested that normal urine contains insulin^{12,13} but the contention has been refuted by Lawrence.¹⁴ Lessened insulin content of diabetic urine could hardly explain the limited drop in blood sugar when standard amounts of the urine and insulin are injected into rabbits. If such be the case, however, heating the urine should not cause a more marked fall in blood sugar as compared with the effect of unheated urine. Also, if normal urine contains active insulin, the effect of this plus that which is added should result in a more marked fall in blood sugar than in the case of the saline controls. Actual observations prove these suppositions to be untenable.

There is still to be considered the possible influence of some chemical or bacterial constituent of urine upon the activity of insulin. It has been shown that insulin can be inactivated by ammonium hydroxide and other alkalies¹⁵ but estimations of ammonia in the various specimens both before and after heating indicate that variations in this constituent were not the cause of the differences observed in the specimens with regard to insulin effect. Certain bacterial and chemical toxins, e.g., diphtheria toxin and histamine, are reputed to have a deleterious influence upon the activity of insulin.^{16,17,18} It is a matter of practical experience that diabetics do badly in the presence

of infection. It is uncertain as yet exactly how infection exerts its influence in these cases, whether it is a matter of direct neutralization of insulin by the toxins produced by the bacteria, the elaboration of some chemical substance possessing anti-insulin properties, for example, some protein-split product, the passage into the blood stream of trypsin as the result of altered permeability of the endothelium of the blood vessels of the pancreas as suggested by Epstein and Rosenthal,⁴ or whether it is due to stimulation of certain glands of internal secretion, whose products are antagonistic to insulin such as the thyroid and the adrenals as favored by Lawrence and Buckley.¹⁷ The possible influence of some of these factors has been discussed already but with regard to the effect of any bacteria in the samples of urine employed in these tests, gross contamination was not permitted. On several occasions, cultures were made from the sediment of the centrifuged samples and suspensions of the organisms obtained by washing the surface of the media with normal saline. To these concentrated suspensions, insulin was added and injections made into rabbits in the same manner as in the tests described above. While there was evidence of slight insulin inhibition it was obvious that the presence of any bacteria or bacterial toxins ordinarily present in the urine could not account for the whole of the inhibitory effect exhibited by urine. This is rather in agreement with the findings of Sweeney¹⁹ who concluded that toxemia produced by diphtheria toxin in animals had little, if any, effect upon the action of injected insulin. His deduction was

that toxemia influenced carbohydrate metabolism by impairment of the animal's ability to store carbohydrate due to a suppression of the production of endogenous insulin.

The observation that insulin inhibition was more evident with diabetic urine than with non-diabetic urine in certain cases, but not in all, calls for some comment. Undoubtedly this substance, whatever it is, which is responsible for the inhibitory effect is an elusive body. If it is representative of something in the blood which has a pathogenic influence in certain diabetics, as pointed out above, there is reason for believing that it would operate to a greater degree in some cases than in others, and there is as yet no sure way of identifying the cases in which it would be most likely to be encountered in blood or urine.

SUMMARY AND CONCLUSIONS

1. A relatively small series of observations points to the presence of a substance in urine which causes partial inactivation of insulin when the latter is added to the urine, incubated and the effect of the insulin upon the blood sugar of the rabbit noted following subcutaneous injection of the mixture.

2. The urine of diabetic patients appears to possess the insulin-inhibiting property to a slightly greater degree than does the urine of non-diabetic hospital patients and normal persons. The difference is most marked in patients with severe diabetes.

3. This insulin-inhibiting factor is destroyed by heating the urine at 60°C. for several hours or by boiling the urine for a few minutes previous to the addition of the insulin.

4. It is assumed that this substance enters the urine from the blood stream by elimination through the kidneys. Whether or not it is identical with the insulin-inhibiting substance which is believed to exist in the blood of diabetics and of non-diabetics is undetermined.

5. The possible significance of the phenomenon relative to the pathogenesis of diabetes mellitus is discussed.

6. While no definite statement can be made concerning the nature of the insulin-inactivating principle in urine, its behavior with regard to heat suggests an enzyme-like character.

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REFERENCES

- ¹KARELITZ, S., COHEN, P., and LEADER, S. D.: Insulin inactivation by human blood cells and plasma in vitro; effect of normal and of diabetic blood on insulin action, *Arch. Int. Med.*, 1930, xlv, 546-558. Insulin inactivation by human blood cells and plasma in vitro; effect of infection on insulin, *ibid.*, 1930, xlv, 690-701.
- ²WARREN, S.: The pathology of diabetes mellitus, 1930, Lea and Febiger, Philadelphia.
- ³MAURIAC, P., and AUBERTIN, E.: Sur le pouvoir de neutralisation du sang de sujets diabétiques et non diabétiques vis-à-vis de l'insuline, *Compt. rend. Soc. de biol.*, 1928, xcvi, 233-235. Le pouvoir de neutralisation du sang vis-à-vis de l'insuline est d'origine globulaire, *ibid.*, 1928, xcvi, 235-237. Le neutralisation de l'insuline par les globules sanguins est due à une substance anti-insuline intra-globulaire, *ibid.*, 1928, xcvi, 237-238.

- ⁴EPSTEIN, A. A., and ROSENTHAL, N.: Studies on the relation of the external to the internal secretion of the pancreas. II. The effects of trypsin on insulin and its bearing on the causation of diabetes, *Am. Jr. Physiol.*, 1924-1925, lxxi, 316-338.
- ⁵PICKARD, R. J., and PIERCE, L. F.: Accurate blood sugar determinations with one-tenth and five-hundredths cubic centimeters of blood, *Jr. Am. Med. Assoc.*, 1930, xciv, 1134.
- ⁶CULHANE, K.: Use of rabbits in insulin assay, *Quart. Jr. Pharm. and Allied Sci.*, 1928, i, 517-533.
- ⁷VON SCHOENBORN, quoted by WELLS, H. G.: *Chemical pathology*, 5 ed., 1925, W. B. Saunders Co., Philadelphia.
- ⁸WAGO, H.: Antibody production in rabbits following injection with pancreatic ferments, *Jr. Immunol.*, 1919, iv, 19-27.
- ⁹IACONO, G.: External secretion of pancreas in diabetes, *Policlinico*, 1932, xxxix, 133. (Abstr. in *Jr. Am. Med. Assoc.*, 1932, xcvi, 1514).
- ¹⁰LOEWI, O.: Glykämie und Insulin, *Klin. Wchnschr.*, 1927, vi, 2169-2176.
- ¹¹HEDON, M. E.: Existe-t-il dans le sang diabétique une substance à action hyperglycémisante?, *Compt. rend. Soc. de biol.* 1928, xcvi, 564-567. (Abstr. *Presse med.*, 1928, xxxvi, 280).
- ¹²BEST, C. H., and SCOTT, D. A.: Insulin in tissues other than the pancreas; preliminary communication, *Jr. Am. Med. Assoc.*, 1923, lxxxi, 382.
- ¹³PARTOS, A.: Regulation des Kohlehydratstoffwechsels; Ausscheidung des Insulins durch die Nieren und ihre Bedingungen, *Arch. f. d. ges. Physiol.*, 1929, ccxxi, 562-570.
- ¹⁴LAWRENCE, R. D., MADDERS, K., and MILLAR, H. R.: Excretion of insulin in urine, *Brit. Jr. Exper. Path.*, 1930, xi, 117-118.
- ¹⁵WITZEMANN, E. J., and LIVSHIS, L.: The action of ammonium hydroxide and other alkaline compounds upon insulin, *Jr. Biol. Chem.*, 1923, lviii, 463-474.
- ¹⁶TISDALE, F. F., DRAKE, T. G. H., and BROWN, A.: The production of a lowered carbohydrate tolerance in dogs, *Am. Jr. Dis. Child.*, 1926, xxxii, 854-861.
- ¹⁷LAWRENCE, R. D., and BUCKLEY, O. B.: Inhibition of insulin action by toxemias and its explanation; effect of diphtheria toxin on blood-sugar and insulin action in rabbits, *Brit. Jr. Exper. Path.*, 1927, viii, 58-75.
- ¹⁸SWEENEY, J. S., and LACKEY, R. W.: Effect of toxemia on tolerance for dextrose, *Arch. Int. Med.*, 1928, xli, 257-263.
- ¹⁹SWEENEY, J. S.: Effect of toxemia on tolerance for dextrose and on action of insulin, *Arch. Int. Med.*, 1928, xli, 420-427.

Observations on Human Adrenals with Especial Reference to the Relative Weight of the Normal Medulla*

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DESPITE the immense amount of work that has been done on various problems that have to do with the suprarenals, the question as to the weight of an average, fresh, normal gland still remains in doubt and no figures whatever are as yet available as to the weight of its medulla. Now to be sure, insofar as the first question is concerned, it is possible to set up a tentative average value by means of data to be found in the literature of the subject. For example, this can be done simply by combining the figures contained in the papers of Dietrich and Siegmund¹ and Materna.² This procedure, which brings together the experimental results of fourteen workers, yields a mean value of 12.3 grams for both adrenals or a value of slightly more than 6 grams for a single gland. However, it would appear that this figure is much too high. For Materna,³ on weighing presumably normal suprarenals secured from the bodies of twenty-five persons who had suffered violent deaths—eleven were those of suicides—found that the average weight of a single gland was approximately 4.5 grams; whereas with

glands removed from forty pathological subjects, he⁴ obtained the following average values for the left adrenal: in twelve cases in which death had been caused by various circulatory conditions, 5.8 grams; in twenty average hospital autopsy subjects, 6.2 grams; and in eight subjects with various septic diseases, 8.4 grams. Having found experimentally that more or less profound changes in the normal relation of the watery and lipid elements of the suprarenal gland are characteristic of certain disease processes, Materna believes that this variable factor is chiefly responsible for the seemingly discrepant weight findings just described.

In regard to the second question—that as to the weight of the normal medulla—it should perhaps be stated in passing that Elliot and Tuckett,⁵ by means of planimeter measurements made with serial sections, determined the amount of medullary tissue in the left suprarenal glands of two rats and found that the medulla formed 9 per cent of the gland in a male rat of 120 grams, and 6 per cent in one of 190 grams; and that Donaldson,⁶ who examined by a similar method the supra-

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renal glands of seventeen albino rats, got a mean value of 8.4 per cent for the ratio of the volume of the medulla to that of the whole gland.

Such, it would seem, are some of the principal facts now available as to the two points under consideration.

In this paper a brief account is given of various data obtained during an experimental study of human adrenal glands. However, the main object in view was to determine if possible the relative mass of the normal medulla by dissecting it out and weighing it as a separate structure.

MATERIAL

All of the data used in the preparation of this paper were obtained in the autopsy department of a coroner's office, by means of postmortem examinations carried out among the unknown dead of a large city. These examinations were made from three to five times weekly during a period of nearly five months.

In the great majority of cases the subjects utilized were those of persons who had met death suddenly through violence of some sort—for example, in automobile accidents or through falls, blows, crushing injuries, or gunshot wounds. However, in five instances accidental drowning was the cause of death and there were a few cases of suicide. In all nearly 100 pairs of glands were examined. Since, for reasons that will appear later, occasionally it seemed advisable to reject suprarenals obtained from subjects that appeared to be normal and since, for comparative purposes, many of the glands examined were those found in the presence of various pathological

states such as occur, for example, in cardio-renal disease, in pneumonia or in septic infections only fifty pairs of glands are included in our series.

In regard to the question as to the sex factor, it may be stated that of the fifty normal subjects, forty-one were males and nine were females. The question as to the age factor cannot be answered definitely. However, the estimated age values of the fifty normal subjects ranged from seventeen to sixty-two years and gave an average of 39.7 years.

The general findings made in the course of this study have now to be considered. As several kinds of data must be dealt with, it will be convenient to describe in the following pages (1) certain factors that appear to modify the shape of an adrenal gland, (2) some data obtained by micrometer measurements, (3) the isolation of the medulla, and (4) the experimental results.

FACTORS THAT MODIFY THE FORM OF THE SUPRARENAL GLAND

Subcapsular Location of the Gland. Bartlett⁷ described this as "a rare condition in which the adrenals lie in part or entirely in direct apposition with the kidney parenchyma with no intervening capsule". In his case both of the adrenals were firmly adherent to the kidneys though this condition was more marked on the right than on the left side. He found that the right suprarenal measured 45 mm. vertically by 50 mm. in width at its widest part. As both glands were to be examined histologically, they were not weighed.

Other cases of subcapsular location of the suprarenals have been reported

by Apert and Vallery-Radot⁸ and by Omelskyj.⁹ Having observed heterotopia of the suprarenal in the kidney no less than four times, Omelskyj remarks "that in comparison with the frequency of this phenomenon it is astounding how rarely it is mentioned in the literature". Regarding the question as to what portion of the adrenal surface is prone to unite with the kidney substance, he noted that in each instance the adrenal was attached only at its under extremity. Many of these glands, he states, appeared to be very much enlarged.

Two cases of unilateral, right adrenal-renal heterotopia were examined in the course of this study. The bodies of the subjects concerned were those of powerfully built men who had suffered violent deaths apparently while in a state of perfect health—in one case from a fracture of the skull, in the other from a penetrating wound of the throat. In each instance the lower extremity of the right suprarenal was embedded to the depth of several millimeters in the substance of the kidney; so firm indeed was the union between the two tissues at this point that the gland could be separated from the kidney only by cutting deeply into the parenchyma of the latter organ. These glands were unusually large and in each one the tissue seemed to be thinned out in places. They were extremely bizarre in shape. Neither one is included in the normal series listed in table 1. Expressed in millimeters, the length and width measurements of the two glands were, respectively, 69 by 46, and 45 by 55. In grams, the weights of each whole gland and its

medulla were, respectively, 7.029–.765 and 6.475–.740.

On the whole, such as it is, the foregoing evidence seems to indicate that, when it is adherent to the kidney, the suprarenal gland gradually becomes pulled out of shape and enlarged—particularly in its transverse measurement. It may be added, as of some interest in this connection, that no distortion of the suprarenal was noted in those cases—and this condition was encountered a number of times—in which the gland was firmly united with the under surface of the liver.

Absence of One Kidney. This appears to be a rare condition. Guizzetti and Pariset¹⁰ found that one kidney was absent in 39 out of 20,000 autopsies. However, the statistics as to the incidence of this condition vary widely. Other authorities assign values that run as high as 1 in 4,000. Usually it is the left kidney that is missing.

What effect does the absence of one kidney have upon the shape of the corresponding suprarenal gland?

Miloslavich¹¹ answers this question by stating that, in such a case, the suprarenal is rounded in form and that neither of its surfaces exhibits the indentations and longitudinal ridges that usually characterize this gland. It is not to be denied, he affirms, that under normal circumstances the kidney and the liver offer a resistance to the suprarenal that probably exerts some influence upon its configuration. However, his paper contains no autopsy data obtained from cases of renal aplasia.

In a case of absent left kidney de-

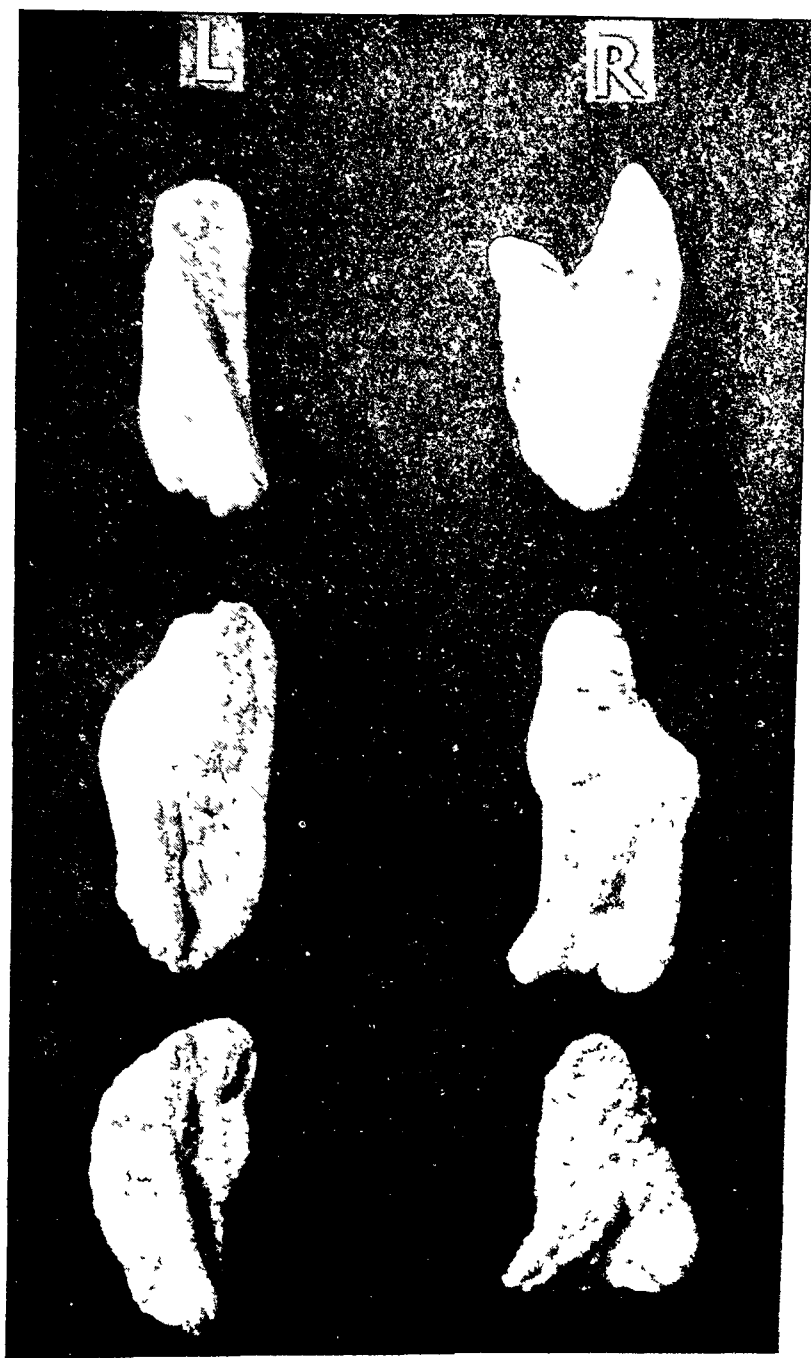


FIG. 1. Normal adult adrenals photographed in the fresh state. Note pressure-ridge on each one.

scribed by Lucksch¹² the left adrenal was rounded in form and exhibited none of the usual surface markings. It measured 38 by 35 millimeters. The two glands weighed in the fresh state 10.5 grams. Curiously enough they were joined together by a narrow isthmus.

Congenital absence of the left kidney was noted in one of the normal

cases reported in this paper. The cadaver in question was that of a bandit, a man in the early fifties, symmetrically developed and athletic in type. The cause of death was a gunshot wound of the heart. In the course of the postmortem examination it was discovered that the left kidney was missing. Otherwise, however, nothing of importance was noted. The right

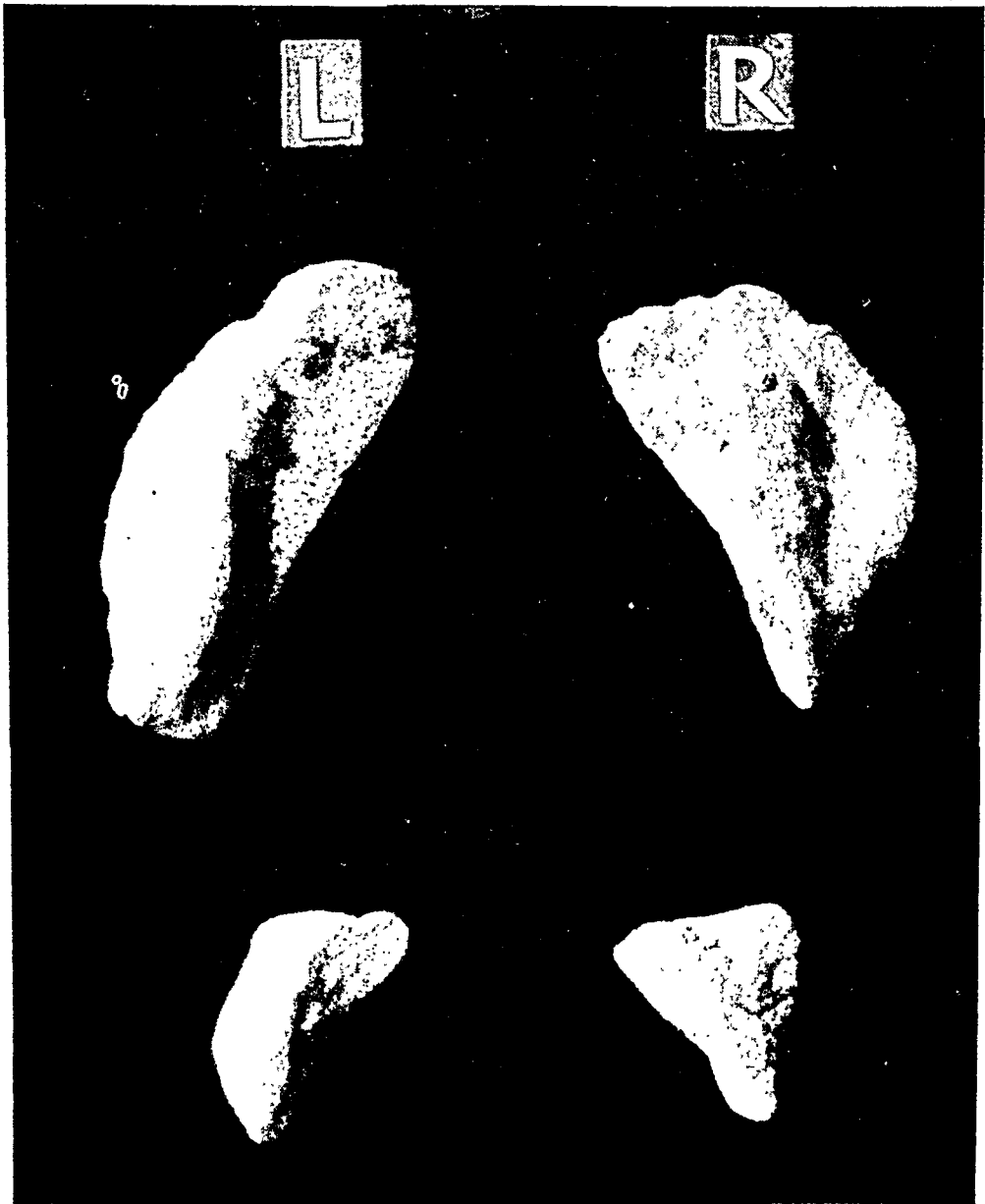


FIG. 2. Adrenals of normal infant four months old compared with adrenals of adult. Measurements of infant's adrenals: left 33 mm. by 9 mm.; right 28 mm. by 22 mm. Weights: left 0.939; right 0.963 gram.

kidney appeared to be perfectly normal. Unfortunately it was neither measured nor weighed. The left suprarenal was in the normal location, concealed—as it usually is—amid layers of fat. When dissected free, it was found to have a rounded, almost disc-like, form and to be almost entirely devoid of surface markings. However, both its color and its consistency were normal. Figure 3 (A-2) shows the medulla of this gland as it appeared after it had been hardened in formaldehyde solution. The other medulla (A-1) is that of an average normal left suprarenal gland. Further details concerning the adrenals of this subject are given elsewhere. (Table 1, No. 6.)

It will be noted that the findings made, both in Lucksch's case and in the one here reported, substantiate Miloslavich's opinion: namely, that when one kidney is congenitally absent the corresponding suprarenal gland is nearly round in shape and almost smooth on both of its surfaces. However, topographically speaking, it may be pointed out that such an unmodeled gland appears to be chiefly remarkable because of the absence of the prominent flange-like ridge that invariably marks the posterior surface of an adrenal when its kidney is in situ. The five pairs of glands shown in figures 1 and 2 give a fair idea as to the form of this ridge and as to its orientation. Incidentally, it should be remarked that these glands were photographed in the fresh state immediately after they had been weighed. It will be observed that the concavity of the ridge faces the inferior border of the gland and that, instead of lying in the prin-

cipal axis of the gland, the ridge crosses the adrenal obliquely.

The question as to when this peculiar elevation first makes its appearance seems to be unanswerable. But the fact that the ridge is present in typical form in the fourth month of infancy (figure 2), seems to indicate that it must be thrown up at a very early period, perhaps even before the onset of the cortical involution process. Almost equally unanswerable, it would seem, is the query as to how the ridge is formed. In this connection, however, it may be stated that there is some objective basis for the supposition that it is formed by pressure, since fairly numerous measurements made in the course of this study show that the inferior border of an adrenal gland is usually, if not invariably, much thinner than its superior border. This subject is treated more fully in the next section.

DATA OBTAINED BY MICROMETER MEASUREMENTS

Before proceeding to describe the measurement data, attention may be called to certain physical peculiarities that appear to be characteristic of normal and of pathological adrenals.

Physical Characteristics of Normal Adrenals. As a prefatory note, it should perhaps be remarked that unless great care is exercised during the autopsy the suprarenals are apt to be cut or torn. So greatly does the normal suprarenal resemble, both in color and consistency, the tissue in which it lies embedded that, even in a laboratory dissection, it was often no easy matter to find the gland in the collop of kid-

ney substance and fat obtained at the postmortem examination.

Careful notes on the subject kept throughout this study seem to show that in any given case there is no correlation between the size of the adrenals and the grade of physical devel-

opment. Thus, while it is true that men of outstanding vigor commonly have adrenals that weigh together around 8 grams, it is also true that many strongly built subjects had adrenals that weighed 7 grams or less.

In regard to the question as to the

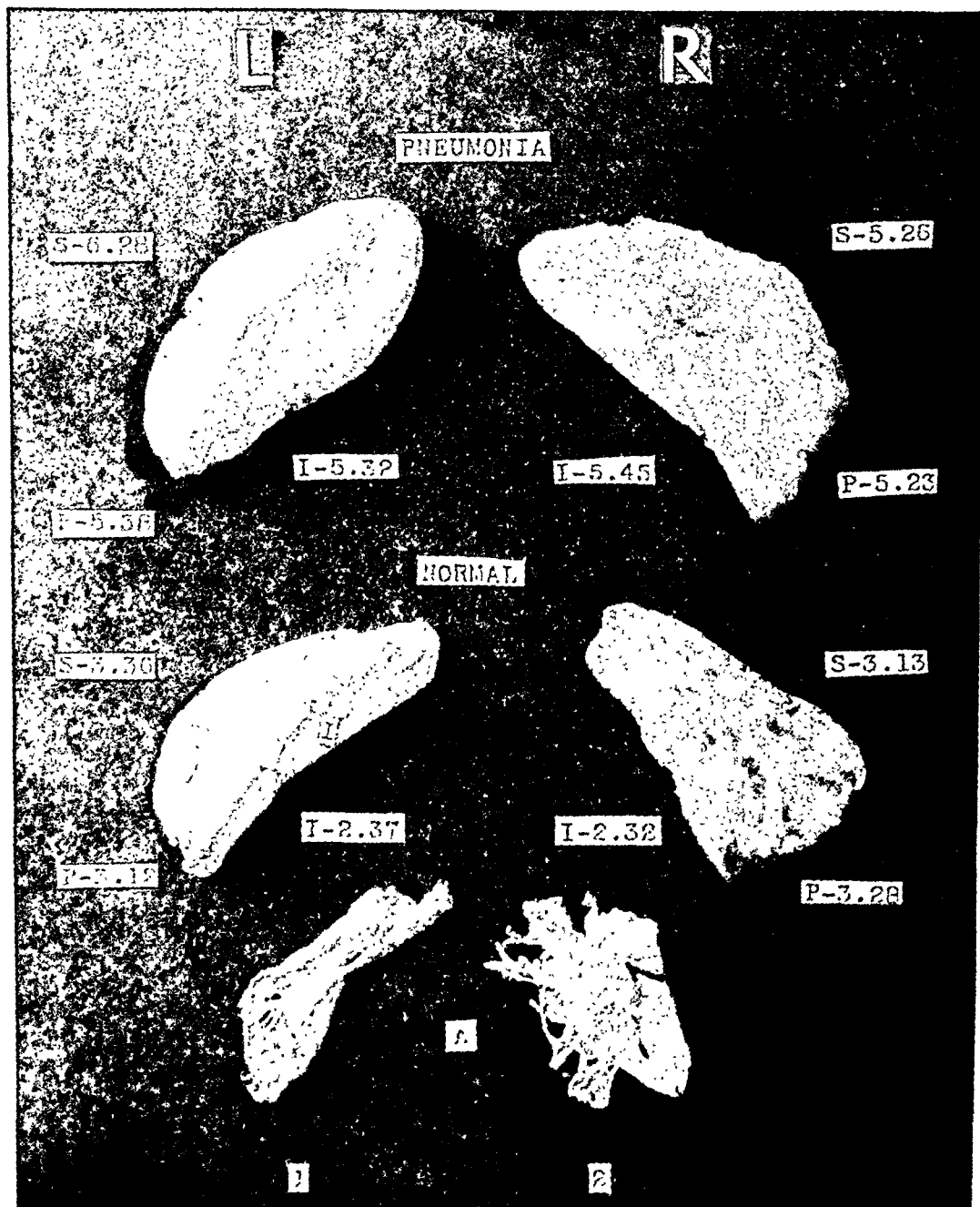


FIG. 3. Normal and morbid adrenals compared. "S"—Superior border. "P"—Pressure ridge. "I"—Inferior border. Pneumonia adrenals weigh 16.0 grams. Normals weigh 6.79 grams. "A"—(1) normal left medulla. "A"—(2) left adrenal medulla in congenital absence of the left kidney.

consistency of a fresh, normal adrenal, it may be stated that such a gland is always limp so that it bends readily over the finger; that it is everywhere soft to the touch; and that its borders as well as its pressure-ridge seem rather delicate and thin. A normal gland is usually brownish-yellow in color. But in two subjects it was noted that the cortical lipoids as well as the abdominal fat were distinctly orange-colored, presumably because of the presence of an excess of carotinoid pigment.

Physical Characteristics of Morbid Adrenals. It seems to be characteristic of the adrenal capsule that it is rather tough to cut, though it tears easily. Hence it may be said somewhat to resemble so-called "dead-rubber". This peculiarity perhaps explains why it is that a suprarenal gland, without exhibiting any very striking changes either in its length or its width, may nearly double in weight. The whole gland appears to swell, as though it had been injected with a fluid of some sort. If this hydration process happens to be minor in degree, there may be nothing remarkable in the appearance of the gland, except that it may seem to have rather thick borders. Extreme grades of hydration, however, produce characteristic changes. The whole gland then has a sodden appearance and its substance feels unusually firm and resistant to the touch. It is often possible to palpate such a gland through the surrounding tissues even though the gland itself cannot be seen. On stripping away the adherent fat from such an adrenal, it will be seen that its surface shows but few of the natural indentations; that its borders, like

those of a mattress, are cushioned or "rolled" and that its pressure-ridge is very broad, especially at the base. These changes in the appearance of the suprarenals were noted most commonly in the presence of pneumonia. For example, in five cases of that disease the average length and width measurements of the adrenals were, respectively, 58 mm. and 28 mm.; whereas the average weight value was 16.2 grams.

Measurement Data. Numerous observations having shown that the superior and inferior borders of the suprarenal gland seemed to differ considerably in point of size, in order to find out how great this apparent difference was, some exact measurements were made. The instrument used was a Starrett micrometer. This instrument reads to hundredths of a millimeter. As this work was undertaken at a rather late stage of the investigation, relatively few glands were measured. Twenty were normal glands and four were obtained from pneumonia subjects. Stated in millimeters, the following average values were obtained for the inferior border, the pressure-ridge, and the superior border, respectively: normal adrenals, 1.8, 2.4 and 2.6; pneumonia adrenals, 4.0, 5.0 and 5.6. However, since these measurements show that the difference was a constant one and that it amounted to approximately one millimeter, they appear to establish the fact that the superior border of the adrenal gland is larger than the inferior border. Typical sets of measurements are shown in figure 3. This figure also illustrates very well, as regards their external appearance, the main points of difference between normal adrenals

and those sometimes found in the presence of pneumonia.

ISOLATION OF THE MEDULLA

Preliminary Note. Here the question as to the practicability of such an undertaking will be touched upon and the surface form of the adrenal medulla will be roughly described.

In regard to the first point, the experimental evidence obtained in the present inquiry seems to show that it is possible to isolate the medulla of an adrenal gland by dissection, provided that the two principal tissues of the gland can be separated from one another along a definite line of cleavage. Experience shows that this sep-

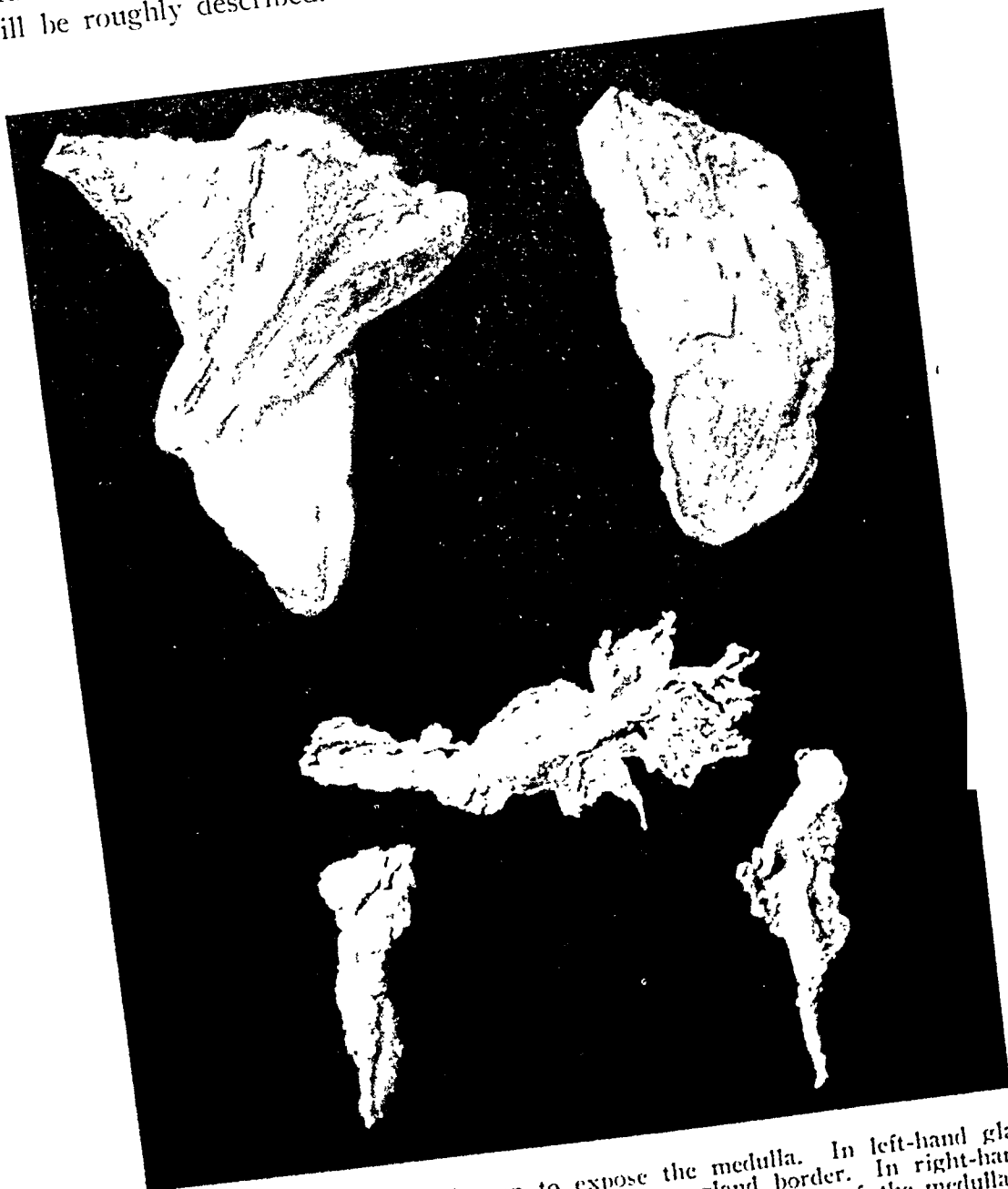


FIG. 4. Normal adrenals laid open to expose the medulla. In left-hand gland note fibrous attachments radiating from tip of medulla to gland border. In right-hand gland the cortex has been partly cut away in order to show arrangement of the medulla. Center figure shows body and membranous portions of medulla. In the two lower figures the membranous portion is curled up from the action of formaldehyde.

aration can be accomplished in about three out of four normal specimens. Naturally, the partition effected is never a quantitative one because of irregularities in the configuration of the medulla. However, with suitable material, it seems probable that the average error is considerably less than 5 per cent.

How is the adrenal medulla arranged within the gland? and what is its general appearance when isolated?

Often simply by inspecting an intact adrenal some idea can be obtained as to the disposition of its medulla. For the surface of a normal adrenal is always marked by irregular elevations (figure 1) and as a rule it is under the most prominent one of these that the main mass of the medulla will be found when the gland is opened. The arrangement of the medulla can also be made out dimly if an adrenal is studied by means of transmitted light. A convenient way to do this is to hold the specimen to be examined up against a 60-watt Mazda light and to observe it through an opening cut in a piece of pasteboard. Under such circumstances, the medullary masses appear as relatively darker areas against a diffuse rosy background.

When it is dissected out and viewed in its entirety, the medulla is seen to consist of two parts—a body and a membranous portion.

Usually the main mass of the body is aggregated about the emergent vein. Its form varies greatly. Sometimes its general shape is that of an Indian arrow-head, but more commonly the body of the medulla is elongated, its length corresponding to that of the pressure-ridge under which it lies.

Commonly, too, one of its extremities tapers to a point (figure 4). The posterior surface of the body of the medulla is always convex and as a rule it is marked by a fine, median longitudinal groove. The medulla is soft and delicate in texture. Its color usually is grayish-white.

The membranous portion of the medulla (figure 4) extends outward from the body of the medulla to the borders of the gland. It is found chiefly in those flat, thin areas of the adrenal where the two opposite cortical surfaces are virtually in direct contact with one another. Very thin and traversed by numerous blood vessels, the membranous portion of the medulla is attached at regular intervals to the periphery of the gland by fibrous trabeculae. Commonly its color is the same as that of the bed of brownish pigment in which it lies.

Dissection. Omitting unnecessary details, the isolation of the adrenal medulla is carried out as follows: A gland having been selected and freed from every bit of adherent fat, the summit of its pressure-ridge is opened by an incision that runs throughout its length. Starting about midway of this incision, the thin process of medullary substance sure to be present within the ridge is sought for and when found is cautiously separated from the adjacent cortical tissue with the aid of a scalpel. At the end of this stage of the dissection a thin, longitudinal fold of medullary substance should stand, nearly erect, in the center of the incision. This fold, which may be likened to a dorsal fin, is now followed on down until the convex surface of the main medullary mass is exposed and

TABLE I

Relative weights of normal suprarenal medullae. The weight determinations were made with glands secured from 50 selected coroner's subjects.

No.	Gland Measurements				Weights in Grams					
	Left		Right		Left			Right		
	Length, Mms.	Width, Mms.	Length, Mms.	Width, Mms.	Whole Gland	Medulla	Medulla %	Whole Gland	Medulla	Medulla %
1	55	19	44	27	3.250	.440	13.5	3.620	.495	13.6
2	44	23	47	23	3.160	.369	11.6	3.035	.339	11.1
3	51	24	53	26	4.519	.439	9.7	3.868	.345	8.9
4	45	25	42	22	3.459	.339	9.7	2.899	.345	11.9
5	53	21	56	23	4.651	.511	10.9	4.302	.453	10.5
6	45	33	51	25	4.214	.621	14.7	4.086	.575	14.0
7	58	20	56	27	4.248	.355	8.3	4.012	.375	9.3
8	48	24	54	32	3.950	.425	10.7	4.275	.460	10.7
9	53	19	50	25	3.980	.469	11.7	4.115	.450	10.9
10	49	30	51	29	4.745	.502	10.5	4.608	.585	12.6
11	46	21	32	30	3.310	.260	7.8	3.322	.340	10.2
12	51	24	50	25	3.529	.285	8.0	4.025	.474	11.7
13	55	25	61	20	3.510	.493	14.0	3.405	.472	13.8
14	40	27	59	35	2.819	.318	11.2	3.595	.368	10.2
15	47	22	41	28	3.878	.370	9.5	3.799	.392	10.3
16	58	23	59	27	3.740	.471	12.5	4.119	.568	13.7
17	49	23	54	33	3.179	.368	11.5	3.395	.469	13.8
18	52	23	48	40	4.883	.437	8.9	4.835	.481	9.9
19	50	25	48	23	4.380	.501	11.4	3.970	.415	10.4
20	54	31	49	23	5.355	.449	8.3	4.573	.390	8.5
21	54	25	51	27	5.419	.505	9.3	5.248	.449	8.5
22	50	21	60	22	3.985	.330	8.3	3.780	.342	9.8
23	56	24	49	30	4.965	.490	9.8	3.782	.358	9.4
24	55	30	48	27	4.874	.460	9.4	3.932	.399	10.1
25	53	24	58	23	4.952	.543	10.9	4.798	.505	10.5
26	52	32	58	30	5.424	.430	7.9	5.915	.535	9.0
27	55	21	48	23	4.719	.505	10.7	3.851	.499	12.9
28	42	14	58	31	2.220	.195	8.7	3.615	.370	10.2
29	50	29	50	28	4.365	.505	11.5	4.399	.498	11.3
30	50	21	42	23	3.902	.431	11.0	3.618	.365	10.0
31	64	18	59	32	4.379	.391	8.9	3.848	.402	10.4
32	58	19	68	34	3.329	.275	8.2	4.761	.438	9.1
33	56	25	51	24	4.419	.398	9.0	4.498	.467	10.3
34	48	19	48	22	3.670	.480	13.0	4.435	.454	10.2
35	57	16	38	27	3.753	.540	14.3	3.452	.415	12.0
36	54	22	59	27	3.439	.278	8.0	3.358	.285	8.4
37	49	20	48	24	4.706	.585	12.4	4.712	.672	14.2
38	59	23	52	25	4.055	.385	9.4	4.622	.499	10.7
39	62	22	65	25	4.099	.569	13.8	5.255	.670	12.7
40	63	22	55	29	4.769	.505	10.5	4.923	.451	9.1
41	62	26	57	32	4.649	.420	9.0	4.372	.432	9.8
42	56	28	62	30	4.730	.435	9.1	5.048	.480	9.5
43	60	20	48	28	4.448	.415	9.3	4.406	.448	10.1
44	49	30	49	34	4.204	.429	10.2	4.571	.561	12.2
45	60	26	51	29	5.775	.535	9.2	5.309	.570	10.7
46	72	14	63	21	4.682	.512	10.9	4.473	.455	10.1
47	57	26	51	29	3.934	.410	10.4	4.289	.455	10.6
48	51	26	65	34	4.282	.415	9.6	4.180	.419	10.0
49	58	22	54	23	3.389	.360	10.6	2.738	.325	11.8
50	55	19	50	32	4.103	.398	9.7	4.019	.412	10.2
Means	53	23	52	27	4.165	.431	10.3	4.161	.448	10.7

the dissection is continued until the entire body of the medulla is laid bare (figure 4). The body of the medulla having been fully exposed, the next step is to begin the work of detaching the whole medulla from its bed. In order to do this, after first cutting the fibres that attach it to the extremity of the gland, the pointed end of the medulla is gently separated from the underlying tissue. It is then folded upon itself and this process of separating and folding is continued until the entire medulla, body and membranous portion, has been dissected out, the adrenal vein being severed last of all. The size of this vessel is often out of all proportion to the size of the gland it serves. In some instances it was found to be no less than 5 mm. in diameter.

The detached medulla should be carefully dried with absorbent paper before it is weighed.

EXPERIMENTAL RESULTS

Since they speak for themselves, little need be said with reference to the results exhibited in table 1. It may be suggested, however, that, even though they are not strictly quantitative, the data as to the weight of the medulla are probably accurate enough for most practical purposes.

As a supplementary note, the fact may be mentioned that in eight of the fifty normal cases pigment spots were

found in the adrenals. In shape the spots were oval or roughly triangular and from 1 mm. to 2 mm. on a side. The largest spot measured 5 mm. by 1 mm. The color was the same in each instance, i.e., a very dark brown. As regards their location, it seems worthy of remark that these spots always were found precisely in the cleavage plane and broadside on to the medulla; but they were invariably on the cortical side of the contact zone. No pigment spots were found in the medulla.

CONCLUSIONS

1. Stated in grams, the weight of a pair of adrenals varied from 5.8 to 11.3. The average value for fifty pairs of normal glands was 8.3.

2. Stated in grams, the average weights of fifty left and fifty right adrenals were, respectively, 4.165 and 4.161.

3. Stated in fractions of a gram, the average weights of fifty left and fifty right adrenal medullae were, respectively, .431 and .448.

4. The medulla appears to form about 10 per cent of the gland.

5. It is pointed out that the superior border of the adrenal gland is larger than the inferior border.

6. Attention is drawn to peculiarities in the configuration of the adrenals that occur (1) in adrenal-renal heterotopia and (2) in congenital absence of the left kidney.

REFERENCES

¹DIETRICH, A., and SIEGMUND, H.: Die Nebenniere und das chromaffine System, in Henke and Lubarsch's Handbuch der speziellen Anat. u. Hist., 1926, viii, 951-1089.

²MATERNA, A.: Das Gewicht der Nebennieren, Ztschr. f. Konstitutionslehre, 1924, ix, 1-5.

³MATERNA, A.: Loc. cit., p. 3.

⁴MATERNA, A., and JANUSCHKE, E.: Ge-

- wicht, Wasser- und Lipoidgehalt der Nebennieren, *Virchow's Arch. f. path. Anat.*, 1927, cclxiii, 537-564.
- ⁵ELLIOT, T. R., and TUCKETT, I.: Cortex and medulla in the suprarenal glands, *Jr. Physiol.*, 1906, xxxiv, 332-369.
- ⁶DONALDSON, J. C.: The relative volumes of the cortex and medulla of the adrenal gland in the albino rat, *Am. Jr. Anat.*, 1919, xxv, 291-298.
- ⁷BARTLETT, C. J.: Direct union between the adrenals and kidneys (subcapsular location of adrenals), *Anat. Rec.*, 1916, x, 67-77.
- ⁸APERT, and VALLERY-RADOT, P.: Capsules surrénales adhérentes au rein, *Bull. et mém. Soc. anat. de Paris*, 1920, lxxxx, 338-344.
- ⁹OMELSKYJ, E.: Zur Nebennierenpathologie; über die an die Niere angewachsene Nebenniere, *Frankf. Ztschr. f. Path.*, 1929, xxxviii, 214-230.
- ¹⁰GUIZZETTI, P., and PARISET, F.: Beziehungen zwischen Missbildungen der Nieren und der Geschlechtsorgane, *Virchow's Arch. f. path. Anat.*, 1911, cciv, 372-392.
- ¹¹MILOSLAVICH, E.: Über Bildungsanomalien der Nebenniere, *Virchow's Arch. f. path. Anat.*, 1914, ccxviii, 131-152.
- ¹²LUCKSCH, F.: Untersuchungen über die Nebennieren, *Beitr. zur path. Anat. u. zur allgem. Path.*, 1916, lxii, 204-226.

Bacteriophage Therapy in Bacillary Dysentery of the Flexner Type*†

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INTRODUCTION

SINCE the suggestion was first made that bacteriophage be used as a therapeutic agent, numerous reports have occurred in medical literature concerning its value. Some of them have been favorable in character, and others less certain as to its beneficial effects. Bacteriophage has been recommended for a great variety of conditions and, indeed, possesses the characteristics required of an ideal germicide in that it is harmless to the body tissues and theoretically destroys the pathogenic organisms. This phenomenon of lysis can be demonstrated easily in vitro with young cultures, but it is doubtful if the results obtained in the animal body by the administration of bacteriophage are always equally phenomenal. Its successful use has been most commonly reported in connection with the gram-negative intestinal bacteria, such as *Shigella*, *Vibrio cholerae*, and *Escherichia coli* and with staphylococcic infections, both cutaneous and systemic in character.

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Unfortunately, however, many of the clinical reports demonstrate but one side of the picture; for instance, one report states that bacteriophage was used in fifty cases—in forty-two with excellent results, in five with mediocre results, and in three with unsuccessful results. No mention is made of control cases and no statements are given that would indicate how the cases might have progressed if the bacteriophage had not been used.

The present report on the use of bacteriophage in bacillary dysentery of the Flexner type represents the results of one group of bacteriophage studies made at the Los Angeles County General Hospital and at the School of Medicine, University of Southern California, during the last two years. Other studies in progress have to deal primarily with its use in typhoid fever and in staphylococcic infections.

METHODS EMPLOYED

During the period of these observations more than one hundred cases of bacillary dysentery have been encountered in the Contagious Unit of the Los Angeles County General Hospital. Only sixty-eight cases are included in the data here presented since only those cases were selected for discussion from which it has been possible, first,

to isolate a bacterium giving characteristic biochemical and serological reactions of *Shigella paradysenteriae*, Flexner type, and, second, to completely lyse the organism isolated with the bacteriophage used in treatment. Cases yielding other strains of bacillary organisms or strains of Flexner type which failed to lyse with our bacteriophage have not been included in this report.

The cases are divided into two groups, first the 1930 series and second the series of patients treated in 1931. In the 1930 series the lytic property of the bacteriophage was tested against each organism isolated before the phage was administered. This caused a delay of several days after admission to hospital before the phage could be administered, since this time was necessary to permit (1) the isolation of the organism and (2) the adaptation of the phage by growth with the organism isolated from the patient.

Since it was found that about 90 per cent of all our Flexner organisms tested were lysed by a single strain of bacteriophage, we decided to employ this strain in the second series and to administer it just as soon after admission as possible. Such administration of bacteriophage immediately after the admission of the patient should be advantageous since it saves the time usually required for routine laboratory procedures in isolation of the organism and for the preparation of the bacteriophage.

Insofar as it was practicable, alternate cases were selected for "phage cases" and for "control cases", care being taken that a phage case and a

control case exhibited as nearly uniform symptoms as possible.

The cases receiving bacteriophage were given a minimum of three doses of bacteriophage by mouth at approximately twelve hour intervals. The dose consisted of from 3 to 5 c.c. of the laboratory prepared broth filtrate which was added to a small amount of unheated water before administration.

Both treated and control cases received the same routine symptomatic treatment which consisted primarily of dietary precautions and methods to limit dehydration.

In children, fluids by mouth were withheld or limited for the first twelve or twenty-four hours, normal saline being given intraperitoneally and by hyperdermoclysis, and glucose intravenously. Following this period fluids were gradually added by oral administration, boiled skimmed milk, lactic acid milk, or protein milk and glucose water being alternated every two hours until the patient had improved sufficiently to receive small amounts of solid food in the form of custards, cereals, cottage cheese, etc.

Adult patients usually received their fluids by mouth, parenteral administration seldom being required. Boiled skimmed milk or buttermilk was allowed during the first forty-eight hours, after which other foods were gradually added. Fats were withheld from both children and adults until stools were normal.

Milk of bismuth or bismuth subcarbonate was given to both children and adults when dysentery was especially marked. Paregoric was allowed in event of severe cramps or tenesmus.

though only one patient in this series received it.

TABLES AND DISCUSSION

In collecting information regarding the cases, special data were assembled concerning the following points: (1) age of the patient, (2) onset and course of the disease prior to hospital admission, (3) temperature, before, during, and after giving bacteriophage, (4) the number and type of stool before, during, and following administration of bacteriophage, (5) special toxic or neurologic symptoms, (6) any unusual complications, and (7) the number of days of hospitalization. The relevant data for comparative purposes are included in the tables.

The number of days of hospitalization has been selected as the most significant criterion for comparison since it represents the most constant standard. It is a general rule that patients with fever are discharged from the hospital three days after a return of the temperature to normal unless other symptoms contraindicate release. In this series of cases the number of stools had also returned to normal before the patient was discharged. Owing to the pressure for admission of patients to the Contagious Disease Unit of the hospital, patients were discharged just as soon as symptoms permitted.

Many mild cases of diarrhea or dysentery caused by bacteria belonging to the genus *Shigella* occur in this region which never become sufficiently severe for hospitalization. Quite commonly within two or three days the patient recovers without special medical attention. If bacteriophage or any other

therapeutic agent were employed in such a group without adequate controls, the results obviously would be interpreted as being favorable. The cases herein recorded, however, represent individuals either who were ill several days at home before coming to the hospital or whose symptoms were sufficiently severe to warrant immediate hospitalization. They, therefore, represent an ideal group for consideration in the testing of any therapeutic measure.

Table 1 gives a summary of the cases treated during the first season when a specific bacteriophage was prepared for each organism. In this series the average number of days elapsing between admission of the patient and administration of the bacteriophage was four. It will be seen that there is no marked difference between the ages, nor between the intensity of symptoms in the group treated with bacteriophage and in the control group; the temperature range, the type of stools, and number of stools per day being about the same in both series. Likewise, the average number of days of hospitalization in each group does not differ markedly, it being 11.9 days for the treated cases and 10.1 for the control series. It is true that the treated cases show a longer period of hospitalization than the control cases, but since bacteriophage was not administered until several days after admission, and since the series was small, it was decided not to lay too much emphasis on the results and to study another series of cases by the second method.

Table 2 gives a summary of the cases treated during the 1931 season when bacteriophage was administered

as soon after admission to the hospital as it was possible to collect a stool from the patient. Organisms recovered from such a stool were later tested for lysis with a portion of the bacteriophage employed and only those cases are recorded in this table where complete lysis occurred. In this series, as well as in the first series, the ages and

fatal cases died during the first twenty-four hours of admission, two having received bacteriophage and one being a control; it seems fair to consider that these reached the hospital too late for any treatment to be of value. The other four fatal cases, two treated and two controls, were of approximately equal intensity. One of the control

TABLE I
SERIES 1930
Table showing Results of Treating Cases of Bacillary Dysentery with Bacteriophage.
(Bacteriophage tested for lysis before administration)

Treated by Bacteriophage given by mouth						Controls					
Patient Number	Age	Maximum Temperature	No. of Stools	Type of Stools	Days in Hospital	Patient Number	Age	Maximum Temperature	No. of Stools	Type of Stools	Days in Hospital
1	1	103	F	Dys.	18	13	2	101	N	Dys.	4
2	3	102	F	Dys.	16	14	2	104	M	Dys.	10
3	1	103	F	Dys.	14	15	2	103	M	Dys.	14
4	2	101	F	Dys.	11	16	4	103	N	Dys.	11
5	2	101	M	Dia.	4	17	7	106	F	Dia.	20
6	3	104	N	Dys.	10	18	9	102	F	Dia.	14
7	3	103	N	Dia.	14	19	12	101	M	Dia.	18
8	5	103	N	Dys.	17	20	18	100	M	Dia.	3
9	5	100	M	Dia.	10	21	22	100	F	Dys.	4
10	6	102	M	Dys.	8	22	57	99	F	Dys.	4
11	21	100	N	Dys.	9						
12	67	101	M	Dia.	10						
Average Days of Hospitalization						10.1					

M (moderate) 4-6 per day; F (frequent) 6-10 per day; N (numerous) 10 per day; Dia—Diarrheic; Dys—Dysenteric (Blood and mucus).

clinical manifestations of the patients in the treated and control groups compare favorably. It will be noted that the average period of hospitalization of the treated group is eleven days, while in the untreated or control group it is 12.1 days, there being a difference of 1.1 days between the two groups.

Though there were no deaths in the 1930 series, there were seven in the 1931 series, four among those treated with bacteriophage and three in the untreated series. Since three of the

cases died in two days as did one of the treated cases, while the other control case died in five days and the other treated case in eight days. It is recognized that the number of fatal cases is too small to be of significance but since there is little difference in the fatalities in the treated and untreated series, significant affirmative evidence for the therapeutic value of bacteriophage is lacking.

D'Herelle, in 1917, first called attention to the presence of a substance

lytic for dysenteric bacteria after having isolated this substance from the stool of a patient convalescing from bacillary dysentery of the Shiga type. In 1926, he further cites in detail sev-

action on the specific bacteria, and it is assumed that lytic action of a bacteriophage assures protection.

With this possibility in mind, some have accepted bacteriophage as a de-

TABLE II
SERIES 1931

Table Showing Results of Treating Cases of Bacillary Dysentery with Bacteriophage.
(Bacteriophage given upon admission and then tested for lysis)

Treated by Bacteriophage given by mouth						Controls					
Patient Number	Age	Maximum Temperature	No. of Stools	Type of Stools	Days in Hospital	Patient Number	Age	Maximum Temperature	No. of Stools	Type of Stools	Days in Hospital
23	1	101	F	Dys.	19	42	1	100	N	Dys.	29
24	1	104	F	Dia.	9	43	1	102	F	Dys.	8
25	1	106	F	Dia.	9	44	1	105	F	Dys.	9
26	1	102	F	Dys.	14	45	2	102	M	Dia.	8
27	2	102	F	Dia.	10	46	2	102	M	Dia.	20
28	3	104	F	Dys.	5	47	5	103	N	Dys.	5
29	3	102	M	Dia.	13	48	3	100	N	Dys.	3
30	4	100	F	Dia.	5	49	3	102	F	Dys.	19
31	4	104	F	Dia.	7	50	3	105	F	Dia.	12
32	4	103	N	Dys.	19	51	1	104	F	Dys.	18
33	4	101	F	Dys.	19	52	5	104	F	Dys.	20
34	5	103	F	Dys.	19	53	5	103	F	Dys.	15
35	6	104	N	Dys.	3	54	6	104	F	Dys.	21
36	7	102	N	Dys.	20	55	7	102	N	Dys.	9
37	19	102	N	Dys.	8	56	9	104	F	Dys.	9
38	20	101	M	Dia.	6	57	20	104	F	Dys.	13
39	20	100	M	Dia.	4	58	30	99	M	Dys.	6
40	26	102	F	Dia.	7	59	32	100	M	Dia.	5
41	41	100	N	Dys.	13	60	47	100	M	Dia.	11
						61	63	101	M	Dia.	12
Average Days of Hospitalization 11						Average Days of Hospitalization 12.1					
Average Days of Hospitalization (1930) 11.9						Average Days of Hospitalization (1930) 10.1					
Average of Both Series 11.45						Average of Both Series 11.1					
FATAL CASES—1931											
62	1	105	N	Dys.	2	66	1	104	F	Dia.	2
63	1	104	N	Dys.	8	67	3	106.6	N	Dys.	1
64	4	105	F	Dia.	1	68	5	106	N	Dys.	5
65	4	106	N	Dys.	1						

eral cases of bacillary dysentery of the Shiga type and shows that bacteriophage lytic for the Shiga bacterium is commonly present in association with the organism. It is suggested that fatalities result from a failure of the bacteriophage to exert a destructive

sirable treatment for bacillary dysentery, especially in those regions where the disease is common in epidemic form. A number of the earlier reports indicated favorable results from its use therapeutically, and with due consideration to these findings the present

study was begun. During its progress a number of recent papers have come to our attention and brief summaries of some of these may be mentioned.

Compton (1929) reports the use of bacteriophage in 66 cases and states the results were very good in 35 cases, good in 10, medium in 6, and a partial failure in 10. He cites no controls in his series.

Burnet, McKie and Wood (1930) in an investigation of 21 cases found that the presence of a highly active phage was generally of favorable import for the patient, though in children of over one year the presence or absence of bacteriophage was not of prognostic significance.

Sen (1930) reports decided success in the treatment of children by bacteriophage.

Asheshov, Taylor, and Morison (1930) in a summary state that in Shiga and Flexner types of bacillary dysentery no effect on the disease is traceable to the administration of bacteriophage. Morison does state, however, that in three epidemics he had 15 deaths in 57 treated cases, and 50 deaths in 92 untreated cases.

London (1930) administered bacteriophage orally to 141 cases of bacillary dysentery; 129 were cured and 12 died. Here again no controls were mentioned.

Riding (1930), in recording the results of 48 cases in which lysis of the organism isolated from the patient was apparent, concludes that bacteriophage is probably quickly eliminated or destroyed and that the clinical course of acute bacillary dysentery is not altered by the oral administration of bacteriophage. He used some of his cases for controls.

Taylor, Greval, and Thant (1930) report a series of 20 controls and 26 cases given 2 c.c. of bacteriophage three times a day and conclude that, in spite of the presence of phage of higher activity in the stools of treated cases as compared with controls, no significant difference exists in the progress of cases either in regard to effect on mortality or as to duration of the period of attack. It is of interest to note that they draw similar conclusions from their controlled series of cholera cases treated with bacteriophage.

Results of the study here reported do not differ from the conclusions of the workers just mentioned who used untreated control cases for comparison. In our series 68 cases are recorded, 35 who received bacteriophage by mouth in addition to symptomatic hospital treatment, and 33 cases who did not receive bacteriophage. The severity of symptoms and ages of patients in the two series compare favorably. It was found (1) that there were four deaths in the bacteriophage treated group and three deaths in the control series and (2) that the average days of hospitalization per patient in the bacteriophage series is 11.45 days while in the control group the average period is 11.1 days.

Conclusions from this study indicate that the oral use of bacteriophage in bacillary dysentery of the Flexner type by the methods here employed does not alter the clinical course of the disease, does not appreciably reduce the number of days of hospitalization, and does not lower the death rate. Continued studies in which larger and more frequent amounts are being given orally in conjunction with bacterio-

phage by retention enema are in progress.*

SUMMARY

1. Sixty-eight cases of bacillary dysentery from which *Shigella paradysenteriae* of the Flexner type was isolated are considered in a study of bacteriophage therapy.

2. Thirty-three of the cases received no bacteriophage and are therefore used as controls.

3. Twelve of the treated cases appeared in the 1930 season when a specific bacteriophage was prepared for each case. Such phage was administered by mouth, an average of four days after admission to hospital. The average number of days of hospitalization of this group was 11.9 days

while in the control group for the same period the average was 10.1 days. No deaths were recorded in either series during this season.

4. Twenty-three cases in the 1931 series received a bacteriophage which was later tested for lytic properties. Such bacteriophage was administered by mouth within a few hours after admission to hospital. The average number of days of hospitalization of this group was 11 days while in the corresponding control group, the average period of hospitalization was 12.1 days. There were four deaths in the bacteriophage treated series and three in the control series during this season.

5. These results indicate that the oral administration of bacteriophage, as used in this study, produces no marked clinical benefit over the recognized symptomatic care and treatment.

*These studies were continued during the 1932-33 season when amounts of bacteriophage ranging from 50 to 100 c.c. were given by retention enema to each patient in addition to the bacteriophage by mouth. The treated series shows a hospitalization period of 12.3 days and the control series one of 12.5 days. These continued observations do not alter the previous conclusions.

Doctors M. F. Bigler, E. M. Kittredge, and Ruth Anderson have coöperated in this work by supervising the clinical studies. Their assistance has been greatly appreciated.

REFERENCES

- ASHESHOV, I., TAYLOR, J., and MORISON, J.: Recherches sur le bactériophage dans l'Inde Britannique, Bull. de l'Office internat. d'hyg. pub., 1930, xxii, 1882-1892.
- BURNET, F. M., MCKIE, M., and WOOD, I. J.: Investigation on bacillary dysentery in infants, with special reference to bacteriophage phenomena, Med. Jr. Australia, 1930, ii, 71-78.
- COMPTON, A.: Antidysentery bacteriophage in treatment of bacillary dysentery; record of 66 cases treated, with inferences, Lancet, 1929, ii, 273-275.
- D'HERELLE, F.: Sur un microbe antagoniste des bacilles dysentériques, Compt. rend. Acad. d. sc., 1917, 373-375.
- D'HERELLE, F.: The bacteriophage and its behavior, transl. by George H. Smith, 1926, Williams and Wilkins, Baltimore.
- LONDON, J.: Bacteriophage in its clinical aspect, Indian Med. Gaz., 1930, lxxv, 370-371.
- RIDING, D.: Acute bacillary dysentery in Khartoum Province, Sudan, with special reference to bacteriophage treatment; bacteriological investigation, Jr. Hyg., 1930, xxx, 387-401.
- SEN, R.: Treatment of acute bacillary dysentery in children, Calc. Med. Jr., 1930, xxv, 215-219.
- TAYLOR, J., GREVAL, S. D. S., and THANT, U.: Bacteriophage in bacillary dysentery and cholera, Indian Jr. Med. Res., 1930, xviii, 117-136.

Tuberculosis in Officers of the Regular Army*†

By LT. COL. A. T. COOPER, M.C., *Fort Myer, Virginia*

THIS study of officers of the United States Army who have been under treatment for pulmonary tuberculosis at Fitzsimons General Hospital since January 1923 was undertaken in order to assist in arriving at an opinion of the results obtained by treatment of pulmonary tuberculosis in officers on the active list of the United States Army. All too frequently it is the usual opinion throughout the Army that when any officer contracts tuberculosis his days of usefulness for the Army are to a large extent over. Those of us who have been following the officers unfortunate enough to develop chronic pulmonary tuberculosis during their service in the Army have always realized that a large percentage of such officers can be cured and after a suitable period of time return for many years of useful service in the Army.

It is noteworthy that while this group of patients is not large, their progress and disposition have been closely followed over a number of years, as no matter where an officer may be stationed, if clinical pulmonary tuberculosis becomes evident, he is sent to the Fitzsimons General Hospital.

It has been the belief of the Medical

Service at Fitzsimons General Hospital that a large percentage of officers who developed tuberculosis could, after a period of definitive treatment, be returned for active duty to the service. The records of all officers of the Regular Army on active duty who have been admitted to Fitzsimons General Hospital because of chronic pulmonary tuberculosis since January 1, 1923 have been studied. The total number was 102. It was rather a surprise to the investigator to find that the number of officers treated for pulmonary tuberculosis during a period of slightly over eight years was so small.

The following is a table showing the number of officers according to the branch of service and according to grade who have been admitted since 1923 for pulmonary tuberculosis. (See Table I).

It is seen that the junior officers, Captain, 1st Lieutenant, and 2nd Lieutenant, furnish the majority of admissions. Table 2 shows that a higher average percentage incidence of the disease occurs in these grades.

Calculating the percentage of officers admitted from each branch of the service, as is shown in table 3, gives some rather interesting information. It is seen that the Medical Corps stands out with a very much higher percentage of admissions than any

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†From the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

TABLE I
Officer Patients

Branch of Service	Total Number	Grade					
		Col.	Lt. Col.	Major	Captain	1st Lt.	2nd Lt.
Infantry	27			1	12	8	6
Engineers	4			1	1	2	
Quartermaster Corps ...	6		1		1	4	
Field Artillery	14			1	5	6	2
Coast Artillery Corps..	11			2	4	4	1
Cavalry	6	1	1		2	2	
Air Corps	14			2	1	8	3
Medical Corps	14	1	3	3	7		
Dental Corps	2			1	1		
Veterinary Corps	1			1			
Judge Advocate General's Department	1			1			
Chaplain	1				1		
Signal Corps	1				1		
Total	102	2	5	13	36	34	12

TABLE II

	Strength in Army	Admitted to F.G.H. with pul. tbc.	Percentage
Colonels	485	2	.004
Lieutenant Colonels	593	5	.008
Majors	1898	13	.0068
Captains	3710	36	.0097
1st Lieutenants	2863	34	.012
2nd Lieutenants	1805	12	.0066

TABLE III
Percentage of Officers from Each Branch of Service

Branch	Strength	Pul. Tbc.	Percentage
Infantry	4200	27	.0064
Engineers	600	4	.0066
Quartermaster Corps	1054	6	.0057
Field Artillery	1900	14	.0074
Coast Artillery Corps	1200	11	.0092
Cavalry	950	6	.0063
Air Corps	1518	14	.0092
Medical Corps	983	14	.0142
Dental Corps	158	2	.0126
Veterinary Corps	126	1	.0079
Judge Advocate General's Department....	115	1	.0087
Chaplain	125	1	.008
Signal Corps	300	1	.0033

other branch of the service, with the Dental Corps a close second. No comment is made on the possible reasons why Medical Corps and Dental Corps

officers should be more prone to develop chronic pulmonary tuberculosis than officers in other branches. However, the data as obtained are herewith

TABLE VI
First Disposition of Cases

Rank	Total No.	Average age, Yrs.	Duty	Retired	Died	Still in hospital	Transferred
Colonel	2	54	0	0	0	1	1
Lt. Col.....	5	48	5				
Major	13	39	9	3	0	1	
Captain	36	36	17	7	6	6	
1st Lieut.	34	32	11	14	3	6	
2nd Lieut.	12	26	2	5	1	4	
Total	102		44	29	10	18	1

to Fitzsimons General Hospital, forty-four were at their initial disposition returned to duty, this being approximately 43 per cent.

It is to be expected, of course, that a certain number of officers who are returned to duty with chronic pulmonary tuberculosis will have relapses, and table 7 shows that of the forty-four officers who, having been hospitalized for tuberculosis, were returned to duty, twenty were readmitted to Fitzsimons General Hospital because of reactivation of their pulmonary lesions. Eleven of these twenty were again returned to duty, so that of the original 102 officers, thirty-four are now on active duty. Table 7 shows the number of officers by grades who were readmitted and their disposition. Twenty-four of the forty-four officers are still on active duty and have never been returned to the hospital as patients.

The present condition of the thirty-three officers who have been retired to September 1, 1931, as to whether living or dead, is shown in table 8.

TABLE VIII

Rank	Number	Living	Dead
Colonel	0		
Lt. Col.....	0		
Major	4	3	1
Captain	8	8	
1st Lieut.	16	12	4
2nd Lieut.	5	4	1
Total	33	27	6

This table (8) shows that the majority, 81.9 per cent, of these officers are still living and that 18.1 per cent died.

Table 9 shows the final disposition of all cases of pulmonary tuberculosis up to September 1, 1931 as to whether they have been returned to, and remained on duty, whether they were eventually retired, or whether they died. These are the final figures that

TABLE VII
Disposition of Active Duty Officers Readmitted to the Hospital for Pulmonary Tuberculosis

Rank	Number	Duty	Retired	Died	Still in hospital	Transferred
Colonel	0					
Lt. Col.....	3	1			1	1
Major	4	3	1			
Captain	7	4	1		2	
1st Lieut.	6	3	2		1	
2nd Lieut.	0					
Total	20	11	4	0	4	1

can be calculated to September 1st and show that thirty-four, or 33.33 per cent, have been returned to duty and have remained on duty; twenty-eight, or 27.45 per cent, have been retired; seventeen, or 16.66 per cent, have died. This includes all officers who died on active duty and who died after being retired.

showed both a cavity and, at some time or other, a hemorrhage. Fifty-three, or 51.96 per cent, had cavities but no record of hemorrhage, and five had a hemorrhage without demonstrable cavity.

The disposition of the officers having these complications is shown in table 11. Fifty per cent of those hav-

TABLE IX
Final Disposition of Officers

Rank	Number	Remained on duty	Eventually retired	Died	Still in hospital	Transferred
Colonel	2	2	1	1	1	1
Lt. Col.	5	8	3	1	1	
Major	13	14	8	6	8	
Captain	36	8	12	7	7	
1st Lieut.	34	2	4	2	4	
2nd Lieut.	12					1
Total	102	34	28	17	22	

Those of us at Fitzsimons General Hospital who have followed the progress of chronic pulmonary tuberculosis in individual cases have realized that cavities and hemorrhages are serious complications and that unless hemorrhages are controlled and cavities are obliterated by some form of collapse therapy, the prognosis in the case is rather grave as to ultimate recovery.

Table 10 shows that fifteen, or 14.7 per cent, of these officers had hemorrhages, and that 61.76 per cent showed cavities; but only 9.8 per cent

ing cavity with a hemorrhage have either died or been retired, three are still in the hospital and only two have been returned to duty. Forty-nine per cent of the officers having a cavity without a hemorrhage have either been retired or died, and 28.3 per cent have been sent to duty. Eleven, or 20.75 per cent, are still in the hospital. This bears out the clinical observation that cavity and hemorrhage are two very serious complications. Of those that had a hemorrhage without any demonstrable cavity, four were returned to

TABLE X
Hemorrhages and Cavities

Age	Hemorrhages		Cavities		Cav. & Hem.	Cav. without Hem.	Hem. without Cav.
	No	Yes	No	Yes			
20-30	18	6	5	19	4	15	2
30-40	48	8	21	35	5	30	3
40-50	15	1	10	6	1	5	
50-60	6	0	3	3		3	
Total	87	15	39	63	10	53	5

duty, one is still in the hospital, and of those who had clinical pulmonary tuberculosis without the occurrence of hemorrhage and without evidence of cavity, 67.65 per cent were returned to duty, 20.59 per cent were retired, and 2.95 per cent died, while 8.82 per cent are still in the hospital.

in this latter table only 28.07 per cent of those showing a positive sputum were returned to duty, 33.33 per cent were retired and 15.79 per cent died, while of those who had negative sputum, 62.22 per cent were returned to duty, 22.22 per cent retired, and 2.22 per cent died.

TABLE XI
Disposition

	Number	Duty	Retired	Died	Transferred	Still in hospital
Cavity and hemorrhage....	10	2	3	2		3
Cavity without hemorrhage.	53	15	19	7	1	11
Hemorrhage without cavity.	5	4				1
No cavity or hemorrhage...	34	23	7	1		3
Total	102	44	29	10	1	18

Table 12 shows the number of officers who had positive sputum and those who had negative sputum. The largest per cent of positive sputa was found in the earlier age periods.

TABLE XII
Sputum

Ages	Number	Positive	Negative
20-30	25	20	5
30-40	55	28	27
40-50	16	7	9
50-60	6	2	4
Total	102	57	45

The disposition of these officers divided into groups on the basis of positive or negative sputum is shown in table 13. It is to be noted that

Table 14 shows the cases grouped in accordance with the types of treatment employed; and table 15 shows the disposition of the groups treated by various measures. The great majority of these patients, 81.37 per cent, either did not require any other therapy than hygienic and rest treatment, or their tuberculosis was so distributed that other therapeutic measures were not feasible.

Table 15 is of interest because it shows that of three cases on which thoracoplasty was done, two were returned to duty. Such a result should be encouraging to those officers upon whom it is necessary to do a surgical collapse. The two officers returned to

TABLE XIII
Disposition

	Number	Duty	Retired	Died	Transferred	Still in hospital
Sputum positive	57	16	19	9	1	12
Sputum negative	45	28	10	1		6
Total	102	44	29	10	1	18

TABLE XIV

Year	Total	Rest & Hygiene	Pneumo-thorax	Thoraco-plasty	Phrenic Exeresis	Phrenic Ex. & Thoraco.	Pneumo. & Phrenic Exeresis	Pneumo. & Thoraco.	Pneumo., Phrenic Ex. & Thoraco.
1923	16	15	1						1
1924	11	9	1				1		
1925	8	8		1		1			
1926	13	13	2	1					
1927	11	7	2	1					
1928	11	7	2		1		2		
1929	8	5	1						
1930	15	13	1						
1931 (to Sept. 1)	9	6							1
Total	102	83	10	3	1	1	3		

TABLE XV
Disposition

	Number	Duty	Retired	Died	Transferred	Still in hospital
Rest and hygiene	83	41	23	7	1	11
Pneumothorax	10	1	3	2		4
Phrenic Exeresis	1		1			1
Thoracoplasty	3	2				2
Phrenic Exeresis and Pneumothorax	3		1			
Thoracoplasty and Pneumothorax				1		
Thoracoplasty and Phrenic Exeresis	1					
Pneumothorax, Phrenic Exeresis and Thoracoplasty.	1		1			
Total	102	44	29	10	1	18

duty are now on protected duty and one of them, at least, is making a very definite and outstanding recovery, so

that there is very little doubt but that at the end of two years he can be marked apparently cured.

Rocky Mountain Spotted Fever*

By G. GILL RICHARDS, M.D., Salt Lake City, Utah

ROCKY Mountain spotted fever may be described as an acute tick-born infectious disease. It was formerly thought to be indigenous to the West where it is most prevalent in the states of Idaho, Oregon, Wyoming, and Montana, but recently cases have been reported from the Atlantic states by Badger, Dyer and Rumreich¹ of the United States Public Health Service. These cases, of which there were forty in Maryland alone in 1931, are clinically and immunologically identical with those seen in the West.

The disease probably existed in the Rocky Mountain region for years before the coming of the white man. Indians feared certain valleys in the late spring and early summer because they felt that these districts were visited by evil spirits and that it was dangerous to enter them during these seasons. Cases of Rocky Mountain spotted fever were discovered in Colorado as early as 1885 but the first medical report was sent to Washington in 1896 by M. W. Wood,² an army surgeon, who collected data from several Idaho physicians treating these cases. In 1899 Dr. E. E. Maxey,³ of Boise, Idaho, published his description of this disease as a distinctly new entity.

In 1902 G. T. McCullough⁴ described a type of the disease in the Bitter Root Valley of Montana which was much more virulent than that seen in Idaho.

In the same year, at the solicitation of the Montana State Board of Health, L. B. Wilson and W. M. Chowning,⁵ of the University of Minnesota, made an investigation as to the nature, cause, and possible means of prevention of this disease. They described an hematozoa which they found in the blood corpuscles of patients and of gophers. They concluded that the disease was transmitted to man by the wood-tick which had become infected from certain rodents. They did not, however, offer sufficient experimental proof of this claim to lead to its general acceptance.

In 1903 J. F. Anderson,⁶ of the United States Public Health Service, studied and classified the ticks of the mountain region. Stiles named the tick, which has been shown to be the chief vector of spotted fever, *Dermacentor andersonii*.

It remained for Howard Taylor Ricketts,⁷ who later sacrificed his life in the interest of medical science, to establish through his painstaking scientific labors the methods by which the relationship of the tick to the disease could be demonstrated. He was able to produce the disease in laboratory

*Read before the American College of Physicians at San Francisco, California, April 7, 1932.

animals by means of the tick. He demonstrated the infected tick in nature and the hereditary passage of the virus from one generation of ticks to the next. He also described a micro-organism whose etiological relationship to the disease was fully demonstrated by Wolbach in 1919.

In 1908 Dr. L. P. McCalla⁸ reported the transmission of the disease from man to man by means of a tick taken from a patient's body and allowed to feed on two volunteers who contracted the disease in four and nine days respectively.

In 1916 L. D. Fricks⁹ described protozoan-like bodies in the red blood cells of patients but hesitated to draw any conclusions as to their etiological significance.

In 1919 Wolbach¹⁰ described micro-organisms which he found in the blood of many laboratory animals and in tissues of ticks infected with Rocky Mountain spotted fever. He named them *Dermacentroxenus rickettsi*.

Noguchi,¹¹ who like Ricketts was later to die in a foreign country of the disease which he was investigating, made many studies of Rocky Mountain spotted fever. He was chiefly interested in attempts to cultivate the microörganism and in the study of immunological reactions. In 1923 he prepared a sero-vaccine which protected the guinea pig against the disease but did not effectively protect the monkey or man.

From 1922 to 1928 R. R. Spencer and R. R. Parker¹² carried on an intensive joint research. Their studies have added many important points to our knowledge of the life cycle of the tick and the maintenance of the virus

in nature. The virus has been shown to exist in an avirulent phase in the fasting tick and to become infective again shortly after the tick has fed. The ability of tick virus to pass through the intact skin has been proved, thus demonstrating how the disease may be acquired without tick bite if infective ticks are crushed in the fingers. The rôle played by other ticks than the *Dermacentor andersonii* in the transmission of the disease from animal to animal has been studied and it has been shown that at least two other species of ticks may be carriers of Rocky Mountain spotted fever virus. To Spencer and Parker is due also the successful development of a vaccine now issued by the laboratory at Hamilton, Montana and shown by several years' experience to be of great prophylactic value.

SEASONAL INCIDENCE

Rocky Mountain spotted fever has occurred in all months of the year but winter cases are very rare. Generally it is most prevalent in the spring from March to June and corresponds to the seasonal abundance of the wood tick. In the higher altitudes it often occurs in the later summer months.

The disease occurs most frequently in those people whose occupation or pleasures necessitates their presence in infected areas in the season of the year when it is most prevalent. Its incidence is therefore more common in men than in women. Children withstand the infection much better than adults. In the regions of high mortality unvaccinated adults past middle life seldom recover.

INCUBATION PERIOD

In man the incubation period is from two to twelve days. Its average duration is from four to seven days. The more virulent the infection the shorter the incubation period. It is also dependent upon the length of feeding time of the infected tick prior to the bite.

SYMPTOMS

Usually the engorged tick can be found still feeding on the patient at the time of the first examination. No lesion develops at the site of the bite, nor is there, as a rule, any enlargement of the regional lymph glands such as is seen in tularemia.

During the prodromal stage of one or two days the patient complains of listlessness, some aches and pains, loss of appetite, chilly sensations, and slight fever. These symptoms progress into a real chill, followed by high fever up to 104 and 105 degrees which lasts fourteen to twenty-one days, with morning remissions, and falls by slow lysis. The pains become general and severe, especially in the back and legs, resembling an early stage of acute articular rheumatism. The calves of the legs become very sensitive and painful to touch or movement. Hyperesthesia of the skin is often very troublesome. Nose bleed occasionally occurs. There is often a slight dry and irritating cough. The conjunctivae are often injected and sometimes hemorrhagic with accompanying photophobia. Gastrointestinal symptoms are not as a rule marked or common. As the disease progresses, the patient usually becomes increasingly anxious and restless. During the height of the fever he is often delirious.

The rash is the most constant and characteristic single sign in the course of the disease. A few patients may, however, die before the appearance of the eruption. The rash is first seen on the wrists, forearms, and ankles, usually appearing on the third or fourth day and gradually spreading to the rest of the body. It begins as a discrete, rose colored, macular eruption which at first disappears under pressure. Later it becomes blotchy and petechial in character. If the rash remains discrete and pinkish it is a favorable prognostic sign. Large spots are more favorable than small ones. The more severe types progress to a darker color, the lesions coalesce and may develop into hemorrhagic and necrotic spots. The life cycle of any given group of spots is about fourteen days, with a gradual change of the lesions to brownish pigmented areas before they entirely disappear. In the more severe types the eruption occurs in the throat and may result in some sloughing. In some cases the rash appears in one, two, or even three crops, each crop running its separate course.

The pulse is often a valuable guide to the condition of the patient. Early in the disease it is slow in proportion to the temperature, and in the milder types it often does not exceed 90 per minute. As the toxemia progresses in the severe forms the pulse becomes increasingly rapid and poor in quality. A rapid pulse is a very unfavorable sign.

Urinary changes are not common except in the older patients who often develop a suppression and die of uremia.

The blood picture is not characteristic. There is a moderate leukocytosis in the first week, increasing up to 15,000 and 18,000 in the second week with a relative increase in large mononuclear cells. Icterus is often a terminal sign in the fatal cases.

DIFFERENTIAL DIAGNOSIS

The disease must be differentiated from typhoid fever, cerebrospinal meningitis, especially the septicemic type, measles, typhus, and even smallpox.

In an area known to be infected the history of tick bite or, as often occurs, the finding of a tick on the patient's body, may lead to an early and an easy diagnosis.

The Weil-Felix reaction has been found to be present in the majority of cases of Rocky Mountain spotted fever, but this does not differentiate it from certain other diseases due to rickettsiae. Immunity tests may be necessary to differentiate it from typhus. Animals which have recovered from typhus are still susceptible to Rocky Mountain spotted fever and those recovering from spotted fever are susceptible to typhus but not to another inoculation of spotted fever virus.

Generally one attack of Rocky Mountain spotted fever produces a permanent immunity against subsequent exposures. There have been a few authentic reports of second attacks.

PATHOLOGY

The gross pathology is not distinctive. The subcutaneous hemorrhages and enlargement of the spleen are the only constant and striking macroscopic

lesions. The lymph glands are enlarged in some cases.

Microscopically there is a perivascular infiltration of the subcutaneous tissue and the small blood vessels may be completely occluded with mononuclear cells. In the endothelial and smooth muscle cells of the media, large numbers of the minute rickettsiae bodies were first described by Wolbach and have subsequently been confirmed by others. Wolbach¹⁰ considers spotted fever as a disease of the peripheral blood vessels or an acute endangitis.

COMPLICATIONS AND MORTALITY

Sloughing of the soft parts in the mouth or of the scrotum occasionally occurs with secondary infections. Phlebitis is not an infrequent complication. A persistent neuritis lasting for many months was very troublesome in one of my cases. Broncho-pneumonia may develop and be the cause of death. Suppression of urine resulting in uremia is seen in the older patients.

The mortality rate varies greatly in different sections and in different years, ranging from 4 and 5 per cent in the Snake River Valley in Idaho to as high as 90 per cent in some seasons in the Bitter Root Valley in Montana. Death probably occurs from a severe toxemia, which seems to affect chiefly the heart muscle and peripheral blood vessels.

TREATMENT

General treatment should consist of complete rest in bed in order to conserve all possible strength. The patient should be kept as quiet as possible physically and mentally by any safe

measures such as baths, packs, and the use of barbital, phenobarbital, or chloral and bromides, or even morphine if necessary. Cardiac stimulants such as caffeine and digitalis should be given if there is any indication of impending cardiac failure. The intake of fluids and nourishment must be maintained as in any acute fever. If there be nausea and vomiting, as occasionally occurs, fluids may be given by bowel, or subcutaneously.

SPECIFIC THERAPY

Up to the present time there is no specific drug or antiserum. Convalescent serum and transfusions from

convalescent patients have been tried without benefit.

The avoidance of known infected areas during the tick season is the most important prophylactic measure. When of necessity such areas are visited it is important to search the body several times a day for ticks, since their prompt removal in the first hours after attachment may obviate infection. The use of the vaccine as a prophylactic is advised for all whose occupation subjects them to exposure.

The author wishes to acknowledge his indebtedness to Dr. R. R. Parker of Hamilton, Montana for assistance in the preparation of this paper.

BIBLIOGRAPHY

- ¹BADGER, L. F., DYER, R. E., and RUMREICH, A.: Infection of Rocky Mountain spotted fever type; identification in eastern part of United States, Pub. Health Rep., 1931, xlv, 463-470.
- ²SWEET, C. L.; SPRINGER, W. D.; COLLISTER, G.; FAIRCHILD, R. M.; BOWERS, L. C.; DUBOIS, J. K.; FIGGINS, D. W.; and ZIPF, H. (through CAPT. MARSHALL W. WOOD, U. S. A.); Spotted fever as reported from Idaho. Report of the Surgeon-General, U. S. Army, for period ending July 1, 1896. Wash., D. C., Govt. Print. O., 1896, pp. 60-65.
- ³MAXEY, E. E.: Rocky Mountain spotted (tick) fever; with special reference to causal factors, mortality and geographical distribution in Idaho, Med. Sentinel, 1908, xvi, 666-678.
- ⁴MCCULLOUGH, G. T.: Spotted fever, Med. Sentinel, 1902, x, 225-228.
- ⁵WILSON, L. B., and CHOWNING, W. M.: The so-called "spotted fever" of the Rocky Mountains, Jr. Am. Med. Assoc., 1902, xxxix, 131-136.
- ⁶ANDERSON, J. F.: Spotted fever (tick fever) of the Rocky Mountains, Bulletin 14, Marine Hospital Service Hygiene Lab., 1903.
- ⁷RICKETTS, H. T.: The study of "Rocky Mountain spotted fever" (tick fever?) by means of animal inoculations, Jr. Am. Med. Assoc., 1906, xlvii, 33-36. The transmission of Rocky Mountain spotted fever by the bite of the wood-tick (*Dermacentor occidentalis*), *ibid.*, 1906, xlvii, 358. Further observations on Rocky Mountain spotted fever and *Dermacentor occidentalis*, *ibid.*, 1906, xlvii, 1067-1069. The rôle of the wood-tick (*Dermacentor occidentalis*) in Rocky Mountain spotted fever, *ibid.*, 1907, xlix, 24-27. Further experiments with the wood-tick in relation to Rocky Mountain spotted fever, *ibid.*, 1907, xlix, 1278-1281.
- ⁸MCCALLA, L. P.: Direct transmission from man to man of the Rocky Mountain spotted (tick) fever, Med. Sentinel, 1908, xvi, 87-88.
- ⁹FRICKS, L. D.: Rocky Mountain spotted fever, a report of laboratory investigations of the virus, Pub. Health Rep., 1916, xxxi, 516-521.
- ¹⁰VOLBACH, S. B.: Rocky Mountain spotted fever, pathology and etiology, Third Bien. Report Mont. State Bd. Ent., 1919, 55.
- ¹¹NOGUCHI, H.: Experimental prophylactic inoculation against Rocky Mountain spotted fever, Northwest Med., 1923, xxii, 301-303.
- ¹²SPENCER, R. R., and PARKER, R. R.: Rocky Mountain spotted fever; viability of the virus in animal tissues, Pub. Health Rep., 1924, xxxix, 55-57.

The Biological and Clinical Importance of Ovary-Stimulating Hormones*†

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ALTHOUGH it has been recognized for over a quarter of a century that a definite inter-relationship exists between the anterior hypophysis and the gonads, it is only within recent years that it has been possible to study the action of substances which definitely produce anatomical effects in the ovaries. This has been due mainly to the pioneer work of Evans and Long with alkaline extracts of the anterior lobe, and to the experiments of Smith and Engle and Aschheim and Zondek with gland implants in immature animals. These findings have afforded the basis for fundamental biological tests and have led to a vast number of laboratory and clinical investigations. The object of the present paper is to present a brief summary of the more important known facts regarding "ovary-stimulating substances" and at the same time to indicate the trend of modern research in attempting to solve some of the perplexing mysteries of the "female sex hormones".

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DEFINITION AND BIOLOGICAL TESTS

The "ovary-stimulating substances" which form the subject of this paper may best be described by a brief reference to the biological effects that they produce, which form the basis of the laboratory tests employed for their recognition, namely, (1) the stimulation of graafian follicle development with the consequent elaboration of the ovarian hormone "estrin", (2) corpus luteum formation with the production of its hormone "progesterin", and (3) ovulation or follicle rupture.

The first of these effects, follicle ripening, is demonstrated in the immature rat or mouse ovary by means of the Aschheim-Zondek test, and is commonly referred to as "Anterior Pituitary Reaction I", abbreviated to APR I. In addition to the growth of the follicle, however, it is very important to remember that there is also a resultant elaboration of the ovarian hormone "estrin", which manifests itself by a number of important changes. The vaginal outlet of the immature mouse or rat, which is normally closed by a thin membrane, swells and opens. The vaginal mucosa develops from a low cuboidal type of epithelium to a thick, cornified, squamous epithelium, and the cornua of the uterus become markedly hypertrophied.

The second change which may be produced in the immature rat or mouse ovary is an extensive luteinization, a development of granulosa cells into corpus luteum cells. This change is so intense that follicles may become completely transformed into lutein-cell bodies before ovulation has occurred and so produce the histologic picture of "imprisoned ova", the "Anterior Pituitary Reaction III" (APR III) of Aschheim and Zondek. As in the first experiment, this anatomical effect is also accompanied by the production of a hormone, "progesterin", the hormone of the corpus luteum. This likewise results in the opening of the immature vagina, but the mucosa is now not cornified but composed of high cylindrical cells secreting mucus (mucification), while the uterus has acquired the property of responding to an abnormal stimulus and developing a placentoma or deciduoma. The animal, in other words, is in a state of "pseudopregnancy".

In some instances of rats or mice yielding an APR I, it may be possible by delaying sacrificing the animal for a period of twenty-four hours, to demonstrate a rupture of the fully-developed graafian follicle and the presence of ova in the cornua of the uterus. This was very well shown by Smith and Engle¹ with implants of the anterior lobe when they produced a "superovulation" in immature mice. The production of ovulation, however, is more readily demonstrated by the use of rabbits as recommended originally by Friedman.² The ovary of this animal normally contains fully-developed graafian follicles which may be seen grossly as small clear cysts

near the surface of the organ. Following the administration of an "ovary-stimulating substance", such as is found in the urine of pregnant women, a very radical change occurs. The cysts rupture and this process is accompanied by a local hemorrhage, so that within thirty-six hours small, red, protruding areas may readily be seen grossly in the ovaries.*

It is thus apparent that the main function of the "ovary-stimulating substances" is in determining the growth, maturity, and rupture of the graafian follicle, as well as its subsequent development into a corpus luteum. Associated with these anatomical changes there is the elaboration of two ovarian hormones, (1) estrin, which in the human produces a growth of the endometrium, pelvic hyperemia, and turgor of the uterus, and (2) progesterin, which is responsible for the secretory changes found in the pre-gravid phase of the endometrium (figure 1). This hormone (or hormones)† also seems to have a definite influence on lactation (Grüter and Stricker,³ Corner,⁴ Evans and Simpson⁵), and although not entering into the scope of this review it must be remembered that it has an influence on the male sexual organs and so is, more prop-

*In this connection attention must be directed to the presence of hemorrhage into graafian follicles or luteinized cysts which may also be found in rats or mice, and which Aschheim and Zondek refer to as APR II in their "pregnancy test".

†More recent studies by Riddle and his co-workers (Proc. Soc. Exper. Biol. and Med., 1932, xxix, 1211) suggests that there is a separate hormone of the anterior hypophysis, which they call *prolactin*, concerned with lactation.

erly speaking, a "gonad-stimulating" principle rather than merely "ovary-stimulating".

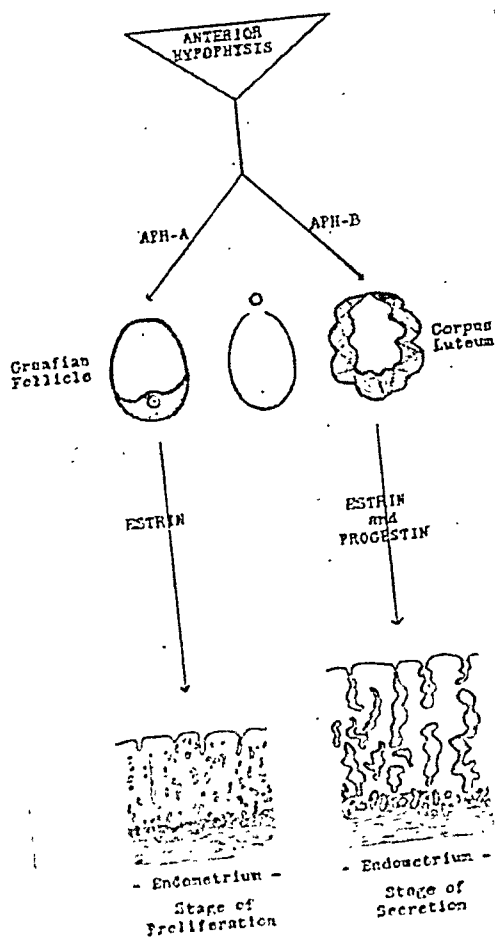


FIG. 1. Diagram illustrating the action of the anterior pituitary ovary-stimulating hormone on the ovaries, with the consequent production of estrin and progesterin.

IS THERE MORE THAN ONE OVARY-STIMULATING HORMONE?

It has been shown that three very definite effects may be assigned to "ovary-stimulating substances", namely, follicle development, ovulation, and corpus luteum formation. The question immediately arises as to whether we are dealing with only one hormone which provokes these reactions in the ovaries, or whether these reactions are

due to two or more hormones each of which has a specific function.

The possibility that there may be two distinct ovary-stimulating hormones was first brought out by an apparent contradiction in the work of Evans and Long, and Smith. The former workers found that the ovarian response of rats to their growth hormone extracts consisted of a delay in the appearance of estrus in immature animals with the formation of abnormal lutein bodies in the ovaries; whereas Smith, and Smith and Engle found that direct implants of the anterior hypophysis produced an early appearance of estrus accompanied by a premature development of normal follicles. In addition, it was found that the administration of Evans' luteinizing hormone inhibited the effect of implants, thus suggesting that not only were two sex hormones concerned but that they were directly antagonistic in their action (Evans and Simpson⁹). The conception of a dual hormone was also advanced by Bellerby,⁷ and later Aschheim⁸ supported this theory on the basis of his findings in numerous biological tests. Since then, most writers on the subject, chiefly in Germany, have assumed the existence of two ovary-stimulating hormones—one termed anteriorpituitary hormone (APH-A), stimulating growth of follicles, and a second (APH-B) responsible for luteinization (Zondek¹⁰). Further evidence in favor of this theory has been advanced in a number of articles (Crew and Wiesner,¹⁰ Evans and Simpson,¹¹ Loeb¹²), and Revold, Hisaw, and Leonard¹³ have reported a method of extracting and separating two gonad-stimulating hor-

mones from anterior lobe tissue. They have found that one of these stimulates follicular growth while the second causes luteinization, and it is of especial interest that the luteinizing hormone they have isolated does not act on the immature ovary unless it has previously been stimulated to follicular activity by the first extract.

There is thus some evidence that there exists more than one ovary-stimulating substance, but on the other hand this conception is not widely accepted as having received sufficient experimental corroboration. It is not generally held that a chemical separation of more than one substance has been clearly accomplished (Dodds¹⁴), and it is possible that the different effects may be due simply to variations in dosage and methods of administration. In a recent extensive report Wallen-Lawrence and van Dyke¹⁵ state that they encountered no evidence of two principles, and further work by Smith and White¹⁶ indicates that under physiological conditions follicular growth and luteinization cannot be explained by the successive secretion of two hormones.

DISTRIBUTION

The development of simple biological tests for the ovary-stimulating substances has resulted in an extensive search for their presence in various organs and body fluids, so that an amazing number of reports are now available on this phase of the subject. In order to simplify an analysis of these findings in the human it would seem advisable to consider them under three separate headings, namely, their occurrence (a) in normal individuals,

(b) during pregnancy, and (c) in pathological conditions.

A. *Normal*. Of primary importance in this work are the findings resulting from the direct examination of the human anterior hypophysis, and it may be stated that both APH-A and APH-B effects have been obtained from the anterior lobes of men and women of all ages and even during intrauterine life (Zondek,⁹ Schultze-Rhnhof and Niedenthal,¹⁷ Siegmund and Mahnert,¹⁸ and others). The same finding applies to animals, as for instance, cattle, sheep, pigs, rats, cats, rabbits and so forth. These observations are of great importance in view of the prevailing conception that the anterior lobe is the main, if not the only, source of the gonad-stimulating hormones.

There is as yet but little known regarding the occurrence of gonad-stimulating hormones in the blood or urine of normal women during adult sexual life. However, a recent study by Zondek¹⁹ shows that by concentrating the urine it is possible to find APH-A at all stages of the menstrual cycle, although the greatest concentration is to be found during the premenstrual phase. In a preliminary communication, Frank, Goldberger and Spielman,²⁰ and Frank²¹ announce that they have conducted similar studies with blood and have also been able to demonstrate APH-A in various individuals, although in this case the greatest concentration has been found early in the cycle, namely between the sixth and ninth days. On the other hand, Neumann and Péter²² report that they find APH-A in the blood at a late stage of the menstrual cycle, between

the twenty-second and twenty-seventh days, so that this phase of the problem must for the present be considered as undetermined.

B. *Pregnancy.* The widespread dissemination of ovary-stimulating hormones in women during pregnancy is one of the most interesting discoveries relating to this work. The test in these cases is characterized mainly by the reaction attributed to APH-B, and forms the basis for the well-known Aschheim-Zondek pregnancy test which has now received worldwide recognition. In addition to urine (Aschheim and Zondek²³) and blood (Fels²⁴; Fluhmann²⁵) positive tests have been obtained from the placenta, decidua, corpus luteum graviditatis, amniotic fluid, fetal blood, tubal mucosa (Aschheim and Zondek²³), colostrum and milk (Heim²⁶), saliva (Trancu-Rainier²⁷), and the serum in blisters resulting from the application of cantharides (Heim²⁸). Closely related to these findings are the strongly positive reactions from the urine of women with hydatidiform mole or chorioepithelioma (Rössler²⁹ and others). However, a remarkable observation was made by Philipp³⁰ and corroborated by Ehrhardt and Mayes³¹ and others, that the anterior hypophysis of pregnant women is practically devoid of ovary-stimulating substances. This would seem to be paradoxical; the significance of this finding will be discussed later.

C. *Pathological Conditions.* In normal individuals the demonstration of ovary-stimulating hormones is a complicated and uncertain procedure, though in pregnancy the tremendous amounts present render it a comparatively simple matter. However, there

are certain endocrinological conditions which are also characterized by the presence of unduly large amounts of these substances in the blood or urine. As the result of the examination of a large series of patients, Fluhmann^{32,33,34} has shown that a definite relation exists between ovarian function as determined by the history of the menstrual cycle and the finding of excessive amounts of ovary-stimulating hormones in the blood. These observations obtained from a large series of patients are listed in table 1, and it is seen that they may be grouped into four categories. The first two are characterized by negative blood tests, and include women with normal menses or with manifestations usually referred to as of "hypo-ovarian" origin, namely, irregular delayed menses, scanty periods, and amenorrhea. In the third group are women in whom there is a total absence of ovarian function, namely castrates, patients in the post-climacteric, and a certain number with prolonged periods of amenorrhea, and it is seen that a large percentage have given positive tests. These findings have received corroboration from the work of Zondek⁹ and Mazer and Hoffman.³⁵ The fourth group also presents a number with unduly large amounts of ovary-stimulating substances in the blood and is of particular interest because it includes a type of patient with symptoms suggesting a possible primary hyperpituitary function.

Zondek³⁶ has drawn attention to similar findings in the urine of women at the time of the climacteric, following castration, and in genital carcinoma. His latter observation is of interest

because he has noted that just as in pregnancy the anterior hypophysis of these patients likewise contains a marked diminution in the amount of stored sex hormones (Zondek³⁷). Neumann³⁸ has found that the urine of children up to the age of ten frequently gives a positive test for the presence of ovary-stimulating hormones.

same characteristics as those made from other sources, such as the urine of pregnant women (Zondek⁹). Although the two ovarian substances, estrin and progestin, are readily taken up by lipoid solvents such as ether and chloroform, this is not the case with the ovary-stimulating hormones which are soluble in alcohol at a concentration of 40 per cent but insoluble

TABLE I

Results of the examination of the blood serum of 266 non-pregnant women for the presence of excessive amounts of ovary-stimulating hormones.

	APR I	APR III	APR I-III	Total Positive	Negative	Total
I. NORMAL OVARIAN FUNCTION						
Regular 28-day menses	0	0	0	0	45	45
II. HYPOHORMONAL CONDITIONS						
Irregular delayed menses	1	0	0	1	29	30
Totally irregular menses	0	0	0	0	15	15
Scanty menses; reg. cycle....	0	0	0	0	16	16
Amenorrhea, short duration..	0	0	0	0	14	14
Amenorrhea, long duration...	0	0	0	0	16	16
III. AFUNCTIONAL CONDITIONS						
Operative castration:						
a. Within 3 mos. postop...	8	0	0	8	12	20
b. After 3 months.....	13	0	0	13	4	17
Radiation castration	8	0	1	9	6	15
Post-climacteric	5	1	3	9	6	15
Amenorrhea, long duration...	5	1	4	10	0	10
IV. HYPERHORMONAL CONDITIONS						
Menopause; irreg. menses ...	9	0	2	11	22	33
Polymenorrhea	5	1	1	7	13	20
	54	3	11	68	198	266

CHEMICAL PROPERTIES

Since it has not yet been possible to isolate the ovary-stimulating principles in pure form, their exact chemical constitution is as yet unknown, but a number of important properties have been determined as a result of the studies of Zondek,⁹ Collip,³⁹ Dickens,⁴⁰ Wallen-Lawrence and van Dyke,¹⁵ Goss and Cole,⁴¹ and others. In the first place, no final chemical differentiation between APH-A and -B has been accomplished, and in the second, extracts made from the anterior pituitary gland have shown essentially the

in concentrations of over 70 per cent. They are also precipitated from an aqueous solution by high-grade acetone, sodium or ammonium sulfate, "colloidal iron" or tannic acid. They are readily adsorbed to charcoal, are destroyed by temperatures above 70°C., and are very sensitive to the action of acids or alkali, since Dickens⁴⁰ noted that 0.2N acid or alkali completely inactivate extracts made from the urine of pregnant women.

An exception must be made in the case of "Emmenin", an estrogenic substance which was isolated by Collip

from the human placenta and which he considers as an ovary-stimulating hormone. This extract is readily soluble in alcohol, is effective when administered orally, and although it causes the appearance of estrual changes in immature rats it only acts on the spayed adult animal in very high concentration. It is evident that this preparation does not fall into the same category as the ovary-stimulating substances under discussion, but it is important to note that Collip also obtains a second principle from the placenta which agrees fairly closely in its general properties to those described above.

Numerous extracts of high potency are now being prepared and used for biological and clinical studies. The anterior lobe has been used as the source of the ovary-stimulating substances by Evans and Long,⁴² Putnam, Teel, and Benedict,⁴³ R  th et al.,⁴⁴ Bugbee et al.,⁴⁵ Reiss et al.,⁴⁶ Bellerby,⁴⁷ Wallen-Lawrence and van Dyke.¹⁵ The urine of pregnant women has yielded large amounts of the hormones and has been employed by Zondek⁹ who gives the name of Prolan to the resultant extract, and by Biedl,⁴⁸ Dickens,⁴⁹ Wallen-Lawrence and van Dyke,¹⁵ Evans et al.,⁴⁹ and others. The human placenta has been employed by Crew and Wiesner,¹⁰ and Collip,³⁹ and potent extracts have also been made from the blood of pregnant women (Fluhmann⁵⁰), and of mares (Goss and Cole¹¹).

SOURCE OF OVARY-STIMULATING HORMONES

Since the first studies on this problem were conducted with the anterior hypophysis, it was natural that this organ should be considered as the sole

source of the ovary-stimulating hormones. However, their wide dissemination has led to some doubt on this question and a number of investigators believe that they may also have an extra-hypophyseal origin. This conception has been advanced by Philipp,⁵¹ Collip,³⁹ Fels,⁵² Motta,⁵³ and others, who claim that the placenta must be considered as capable of manufacturing as well as storing such hormones. The chief arguments advanced in favor of the theory for a placental origin of the ovary-stimulating hormone in the blood and urine during pregnancy may be summarized briefly as follows: (1) The placenta contains very large amounts of an ovary-stimulating substance (or substances); (2) the characteristic histologic pregnancy changes in the anterior pituitary gland of women do not appear until the fifth month of gestation, although large amounts of APH are found very early in the blood and urine; (3) the Aschheim-Zondek test is positive in cases of hydatidiform mole and chorioepithelioma, and becomes negative following the removal of the tumor growth; (4) the anterior hypophysis of pregnant women contains no demonstrable amount of sex hormone (Philipp,³⁹ corroborated by Ehrhardt and Mayes,³¹ Zondek,³⁷ and others); (5) the substance Emmenin which Collip obtains from the placenta, and which he maintains should be considered as an ovary-stimulating hormone, differs from anterior hypophyseal extracts in its chemical properties and in many of its biological effects; (6) some differences in the effects of urine extracts and anterior pituitary implants have been reported, thus suggesting that

they may not be identical* (Engle,⁵⁴ Wallen-Lawrence and van Dyke,¹⁵ Evans et al,⁴⁹ Loeb⁵⁵); (7) the report of Hill and Parkes⁵⁶ and of Reichert et al^{57,58} that urine extracts are relatively ineffective in inducing ovarian changes in hypophysectomized rabbits, dogs, and rats may be interpreted as meaning that these preparations are not hypophyseal hormones since they apparently cannot substitute for this organ.

It would seem that there is evidence in favor of an extrahypophyseal origin for ovary-stimulating hormones, but on the other hand there has been considerable opposition to accepting this theory. In the first place, the presence of the hormones in the placenta by no means necessitates their manufacture there, and it would be just as reasonable to state that ovarian cysts and the mammary and salivary glands also can produce ovary-stimulating substances since they have been found in cyst fluid (Zondek³⁷), milk and colostrum (Heim²⁶), and saliva (Trancu-Rainer²⁷). The characteristic pregnancy changes of the anterior lobe may not be complete until the fifth month, but on the other hand the large amount of hormones in the urine appears so early in pregnancy that some doubt must be expressed as to whether the placenta has sufficiently developed at that stage to produce such quantities (Zondek³⁷). The diminished amounts of ovary-stimulating substances present in the anterior lobe of pregnant women may not mean a lowered production on the part of this gland but an increase in

their utilization by the body so that none remains stored up in the hypophysis (Zondek³⁷). In pregnant cows and pigs there is no hormone demonstrable in the blood or urine, and since there is not the same call for large amounts of this substance as there is in the human, the anterior lobe of these animals has a normal hormone content. The experiments of Collip with Emmenin show that he is dealing with a hormone which apparently has no counterpart in the anterior lobe, and some doubt must be expressed as to whether it can strictly be included in the group of "ovary-stimulating" substances considered in this paper because it does not produce histologic changes in the ovaries of immature rats and is effective in young castrates (Collip³⁹). The biological differences between anterior lobe and urine extracts is an important observation, but is not necessarily conclusive evidence that the hypophysis is not the source of the ovary-stimulating substances. Some of the variable results may be due to differences in dosage, and the preparation of the extracts may possibly cause chemical changes interfering with the normal action of the hormones. This is well illustrated by the experiments of Hill and Parkes⁵⁹ who found that they were unable to induce ovarian changes in hypophysectomized rabbits with urine extracts but could produce this effect fairly readily by the injection of untreated urine.

This question must therefore remain open for the present. It is considered proved that an ovary-stimulating hormone is manufactured by the anterior hypophysis, but the origin and the exact nature of that found in women during pregnancy is not established.

*Since this paper was written a year ago additional evidence has accumulated pointing to biological differences in the ovary-stimulating principles of the anterior hypophysis from those of blood or urine of pregnant women.

THERAPY

It was only natural that as soon as active preparations of this hormone were available, attempts should be made to utilize it as a therapeutic agent. It was also to be expected that it should be applied to the treatment of functional conditions which have generally been considered as of "hypo-ovarian" origin. It is very generally appreciated that there are many difficulties associated with the care of such symptoms and not diseases are treated and that there is an unknown percentage of spontaneous recoveries. In addition, the question of determining proper dosage and methods of administration is one which is as yet unsolved. However, a number of favorable reports dealing with the use of ovary-stimulating preparations in women with amenorrhea, delayed menses, and scanty menses are available (Zondek,⁹ Campbell and Collip,⁶⁰ Seitz,⁶¹ Hirschhardt,⁶⁴ and others) and suggest that this method of approach must be thoroughly investigated. The good results from the injection of whole blood or blood serum from human pregnant donors reported by de Maortua⁶⁵ and Esch,⁶⁶ as well as Zondek's experiments with the extracts⁹ suggest that a solution may be found in the combined administration of ovary-stimulating and ovarian hormones. It is also worthy of note that Zondek⁹ observed a congestion of the pelvic organs and an increase of the temperature of the vagina and rectum following the use of Prolan, and recommends this procedure as part of the conservative treatment of pelvic inflammatory dis-

ease. This is of interest since it has been shown that a much more extensive response of tissue histiocytes to a local irritation can be elicited in the rabbit's uterus when a condition of pseudopregnancy has been set up by the injection of pregnancy urine (Fluhmann⁶⁷).

The most hopeful therapeutic result reported to date, however, is the use of ovary-stimulating extracts made from pregnancy urine or placentae for the treatment of certain types of menorrhagia and metrorrhagia (Martin,⁶⁸ Campbell and Collip,⁶⁰ Novak and Hurd,⁶⁹ Siebke⁷⁰). The large percentage of favorable results which has been obtained by this method for the control of the hemorrhages associated with hyperplasia of the endometrium is very impressive, and it would seem that we now have an effective medical treatment for these patients.

COMMENT

It is thus seen that the ovary-stimulating hormone (or hormones) is a very important factor in the normal physiology of the sexual organs, but it would be hazardous to attempt an exact evaluation of its rôle owing to the obscurity that yet exists as to the interrelationship of the ovaries and the anterior hypophysis. It is evident, however, that it does play a vital part, and as future work yields further information regarding the factors that control the interaction of these glands it will be possible to understand more fully many obscure features concerning puberty, menstruation, pregnancy, and lactation.

On the other hand, it cannot be denied that much progress has also

been made from a clinical standpoint. In the first place, this work has given a new diagnostic procedure, the Aschheim-Zondek test, which has received worldwide approbation and is in general usage. This test is not only highly efficient in recognizing early pregnancy but has been utilized as a control for the successful treatment of chorioepithelioma and hydatidiform mole. Secondly, a more extended use of this test has yielded an additional method of approach for the study of certain endocrinological conditions which are accompanied by disturbances of menstruation. As these investigations are carried further and coupled with studies on the ovarian hormones, there is no doubt that new light will be thrown on the etiology of various disturbances such as amenorrhea, polymenorrhea, and the menopause. And finally, some progress has been recorded from the therapeutic use of ovary-stimulating principles. The results in no way can be said to compare with the hopes and enthusiasm that their discovery initiated, but the mere fact that there is now an effective medical treatment for the uterine hemorrhage accompanying hyperplasia of the endometrium justifies all these endeavors.

SUMMARY

The term "ovary-stimulating hormone" is used for certain biological

substances which stimulate the growth of graafian follicles, ovulation, and corpus luteum formation, resulting in the production of the ovarian hormones estrin and progesterin. It is believed that there are two such hormones, but the evidence is incomplete. The ovary-stimulating principles are chiefly in the anterior hypophysis, but during pregnancy in the human they are widely disseminated in the body of the mother and of the fetus. They have been demonstrated also in the blood and urine of patients with amenorrhea, following castration, and in the post-climacteric period. The evidence obtained to date favors the conception that the anterior lobe of the hypophysis is the main source of these hormones, but it has been suggested that one type may have an extra-hypophyseal origin. From a clinical standpoint, three important advantages have resulted from these studies: (1) the development of an important test for the diagnosis of pregnancy and the control of the treatment of chorioepithelioma and hydatidiform mole; (2) the employment of a new method of approach for the study of certain endocrinological conditions which are accompanied by ovarian disturbances; and (3) the use of extracts of ovary-stimulating hormones for the successful treatment of the uterine hemorrhages accompanying hyperplasia of the endometrium.

REFERENCES

- ¹SMITH, P. E., and ENGLE, E. T.: Experimental evidence regarding rôle of anterior pituitary in development and regulation of genital system, *Am. Jr. Anat.*, 1927, xl, 159-217.
²FRIEDMAN, M. H.: Effect of injections of

- urine from pregnant women on ovary of the rabbit, *Proc. Soc. Exper. Biol. and Med.*, 1929, xxvi, 720.
³GRÜTER, F., and STRICKER, P.: Über die Wirkung eines Hypophysenvorderlappenhormons auf die Auslösung der

- Milchsekretion, *Klin. Wehnschr.*, 1929, viii, 2322-2323.
- ⁴CORNER, G. W.: Hormonal control of lactation; non-effect of corpus luteum; positive action of extracts of hypophysis, *Am. Jr. Physiol.*, 1930, xcv, 43-55.
- ⁵EVANS, H. M., and SIMPSON, M. E.: Hormones of anterior hypophysis, *Am. Jr. Physiol.*, 1931, xcvi, 511-546.
- ⁶EVANS, H. M., and SIMPSON, M. E.: Antagonism of growth and sex hormones of anterior hypophysis, *Jr. Am. Med. Assoc.*, 1928, xci, 1337-1338.
- ⁷BELLERBY, C. W.: Relation of anterior lobe of pituitary to reproductive organs, *Lancet*, 1928, i, 1168-1169.
- ⁸ASCHHEIM, S. (Aussprache): Untersuchungen zur Darstellung des Hypophysenvorderlappenhormons (Zondek), *Ztschr. f. Geburtsh. u. Gynäk.*, 1929, xcv, 371.
- ⁹ZONDEK, B.: Die Hormone des Ovariums und des Hypophysenvorderlappens, 1931, Julius Springer, Berlin.
- ¹⁰CREW, F. A. E., and WIESNER, B. P.: On existence of fourth hormone, thyrotropic in nature, of anterior pituitary, *Brit. Med. Jr.*, 1930, i, 777-778.
- ¹¹EVANS, H. M., and SIMPSON, M. E.: Aschheim-Zondek test for pregnancy; its present status, *Calif. and West. Med.*, 1930, xxxii, 145-148. (Abstr. in *Anat. Rec.*, 1930, xlv, 215)
- ¹²LOEB, L.: Specificity in action of anterior pituitary of different mammals as well as of urine of pregnant women on sex organs and thyroid glands of immature female guinea pigs, *Endocrinology*, 1932, xvi, 129-145.
- ¹³FEVOLD, H. L., HISAW, F. L., and LEONARD, S. L.: Gonad stimulating and luteinizing hormones of anterior lobe of hypophysis, *Am. Jr. Physiol.*, 1931, xcvi, 291-301.
- ¹⁴DODDS, E. C.: Clinical importance of sex hormones, *Am. Jr. Obst. and Gynec.*, 1931, xxii, 520-531.
- ¹⁵WALLEN-LAWRENCE, Z., and VAN DYKE, H. B.: Gonad-stimulating substances of anterior lobe of pituitary body and of pregnancy-urine, *Jr. Pharmacol. and Exper. Therap.*, 1931, xliii, 93-124.
- ¹⁶SMITH, P. E., and WHITE, W. E.: Effect of hypophysectomy on ovulation and corpus luteum formation in rabbit, *Jr. Am. Med. Assoc.*, 1931, xcvi, 1861-1863.
- ¹⁷SCHULTZE-RHONHOF, F., and NIEDENTHAL, R.: Experimentelle Untersuchungen über die Beziehungen zwischen dem Hypophysenvorderlappen und dem Genitale, *Zentralbl. f. Gynäk.*, 1928, xlii, 1892-1895.
- ¹⁸SIEGMUND, H., and MAHNERT, A.: Tierexperimentelle Untersuchungen über die Wirkung infantilen und fetalen Hypophysenvorderlappenhormons auf infantile Keimdrüsen, *Münch. med. Wehnschr.*, 1928, lxxv, 1835-1838.
- ¹⁹ZONDEK, B.: Über die Hormone des Hypophysenvorderlappens; die Ausscheidung des Follikelreifungshormons (HVH-A) im mensuellen Cyclus; der Einfluss der Ovarialtransplantation und der Sexualhormone auf die Ausscheidung des Follikelreifungshormons (HVH-A) nach Kastration, *Klin. Wehnschr.*, 1931, x, 2121-2123.
- ²⁰FRANK, R. T., GOLDBERGER, M. A., and SPIELMAN, F.: Method for demonstrating prepituitary maturity hormone in blood of non-pregnant women, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 999-1001.
- ²¹FRANK, R. T.: Role of female sex hormone, *Jr. Am. Med. Assoc.*, 1931, xcvi, 1852-1857.
- ²²NEUMANN, H. O., and PÉTER, F.: Zur Methodik der Hormonspiegelbestimmung im Blut, *Klin. Wehnschr.*, 1931, x, 2086.
- ²³ASCHHEIM, S., and ZONDEK, B.: Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons; Grundlagen und Technik der Methode, *Klin. Wehnschr.*, 1928, vii, 1404-1411. — Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons; praktische und theoretische Ergebnisse aus den Harnuntersuchungen, *ibid.*, 1928, vii, 1453-1457.
- ²⁴FELS, E.: Die Sexualhormone im Blute, *Arch. f. Gynäk.*, 1927, cxxx, 606-625.
- ²⁵FLUHMAN, C. F.: Anterior pituitary hormone in blood during pregnancy.

- preliminary report, Jr. Am. Med. Assoc., 1929, xcii, 1744-1748.
- ²⁶HEIM, K.: Hormonale Wirkungen der Frauenmilch, *Klin. Wchnschr.*, 1931, x, 357.
- ²⁷TRANCU-RAINER, M.: Über den Gehalt des Speichels an Hypophysenvorderlappenhormonen, *Zentralbl. f. Gynäk.*, 1931, lv, 1971-1977.
- ²⁸HEIM, K.: Hormonale Durchdringung des Körpers in der Schwangerschaft, *Klin. Wchnschr.*, 1931, x, 1031.
- ²⁹RÖSSLER, H.: Über die diagnostische Bedeutung des Hypophysenvorderlappenhormons im Urin in Fällen von Blasenmole und Chorionepitheliom, *Ztschr. f. Geburtsh. u. Gynäk.*, 1929, xcvi, 516-539.
- ³⁰PHILIPP, E.: Sexualhormone, Placenta und Neugeborenes. Experimentelle Studie, *Zentralbl. f. Gynäk.*, 1929, liii, 2386-2394.
- ³¹EHRHARDT, K., and MAYES, B. T.: Beitrag zum Hormongehalt des menschlichen und tierischen Hypophysenvorderlappens, *Zentralbl. f. Gynäk.*, 1930, liv, 2949-2952.
- ³²FLUHMANN, C. F.: Anterior pituitary hormone in blood of women with ovarian deficiency, *Jr. Am. Med. Assoc.*, 1929, xciii, 672-674.
- ³³FLUHMANN, C. F.: Significance of anterior pituitary hormone in blood of gynecologic patients, *Am. Jr. Obst. and Gynec.*, 1930, xx, 1-15.
- ³⁴FLUHMANN, C. F.: Anterior pituitary hormone in blood of women; preliminary clinical classification of results in non-pregnant individuals, *Endocrinology*, 1931, xv, 177-183.
- ³⁵MAZER, C., and HOFFMAN, J.: Three hormone tests for early pregnancy; their clinical evaluation: comparative study, *Jr. Am. Med. Assoc.*, 1931, xcvi, 19-23.
- ³⁶ZONDEK, B.: Über die Hormone des Hypophysenvorderlappens; Follikelreifungshormon (Prolan A)—Klimakterium.—Kastration, *Klin. Wchnschr.*, 1930, ix, 393-396. Über die Hormone des Hypophysenvorderlappens; Follikelreifungshormon (Prolan A) und Tumoren, *ibid.*, 1930, ix, 679-682.
- ³⁷ZONDEK, B.: Hypophysenvorderlappen, HVH, und Placenta. Vergleichende quantitative Untersuchungen bei Mensch und Tier, *Zentralbl. f. Gynäk.*, 1931, lv, 1-12.
- ³⁸NEUMANN, H. O.: Histologische und experimentelle Untersuchungen zur Frage der Schwangerschaftsreaktion der Neugeborenenorgane, *Ztschr. f. Geburtsh. u. Gynäk.*, 1930, xcix, 100-136.
- ³⁹COLLIP, J. B.: Placental hormones, *Canad. Med. Assoc. Jr.*, 1930, xxiii, 631-633.
- ⁴⁰DICKENS, F.: Preparation and properties of gonad-stimulating hormone from urine of pregnancy, *Biochem. Jr.*, 1930, xxiv, 1507-1525.
- ⁴¹Goss, H., and COLE, H. H.: Sex hormones in blood serum of mares; some chemical properties of ovary-stimulating principle, *Endocrinology*, 1931, xv, 214-224.
- ⁴²EVANS, H. M., and LONG, J. A.: The effect of feeding the anterior lobe of the hypophysis on the estrus cycle of the rat, (Abstr.) *Anat. Rec.*, 1921, xxi, 62.
- ⁴³PUTNAM, T. J., TEEL, H. M., and BENEDICT, E. B.: Preparation of sterile, active extract from anterior lobe of hypophysis, with some notes on its effects, *Am. Jr. Physiol.*, 1928, lxxxiv, 157-164.
- ⁴⁴RÄTH, C., HIRSCH-HOFFMANN, H. U., and WULK, H.: Über die Möglichkeit der Darstellung wässriger zu therapeutischen Zwecken geeigneter Lösungen des wirksamen Prinzips des Hypophysenvorderlappens, *Zentralbl. f. Gynäk.*, 1928, lii, 865-866.
- ⁴⁵BUGBEE, E. P., SIMOND, A. E., and GRIMES, H. M.: Anterior pituitary hormones, *Endocrinology*, 1931, xv, 41-54.
- ⁴⁶REISS, M., SELYE, H., and BALINT, J.: Über den luteinisierenden Wirkstoff des Hypophysenvorderlappens, *Endokrinologie*, 1931, viii, 259-262.
- ⁴⁷BELLERBY, C. W.: The physiological properties of anterior lobe pituitary extract in relation to the ovary, *Jr. Physiol.*, 1929, lxxvii, 32-33.
- ⁴⁸BIRDL, A.: Über das Hormon des Hypophysenvorderlappens, *Endokrinologie*, 1928, ii, 241-248.
- ⁴⁹EVANS, H. M., MEYER, K., and SIMPSON, M. E.: Relation of prolactin to anterior hypophyseal hormones, *Am. Jr. Physiol.*, 1932, c, 141-156.

- ⁵⁰FLUHMAN, C. F.: Biological characteristics of ovary-stimulating extracts made from blood of pregnant women, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxix, 1193-1195.
- ⁵¹PHILIPP, E.: Hypophysenvorderlappen und Placenta, *Zentralbl. f. Gynäk.*, 1930, liv, 450-453.
- ⁵²FELS, E.: Über die Bildungsstätten des weiblichen Sexualhormons und des sog. Hypophysenvorderlappenhormons, *Zentralbl. f. Gynäk.*, 1930, liv, 2191-2197.
- ⁵³MOTTA, G.: Über die Theorien von der Bildung der Schwangerschaftshormone vom prähypophysären Typus, *Zentralbl. f. Gynäk.*, 1930, liv, 3096-3101.
- ⁵⁴ENGLE, E. T.: Ovarian responses; differences elicited by treatment with urine from pregnant women and by freshly implanted anterior lobe, *Jr. Am. Med. Assoc.*, 1929, xciii, 276-277.
- ⁵⁵LOEB, L.: Specificity in action of anterior pituitary of different mammals as well as of urine of pregnant women on sex organs and thyroid glands of immature female guinea pigs, *Endocrinology*, 1932, xvi, 129-145.
- ⁵⁶HILL, M., and PARKES, A. S.: Studies on ovulation; action of ovulation-producing substance of urine of pregnancy on hypophysectomized rabbit, *Jr. Physiol.*, 1931, lxxi, 40-46.
- ⁵⁷REICHERT, F. L., and others: Ineffectiveness of prolactin in hypophysectomized animals, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 843-844.
- ⁵⁸REICHERT, F. L., and others: Relative ineffectiveness of prolactin in hypophysectomized animals, *Am. Jr. Physiol.*, 1932, c, 157-161.
- ⁵⁹HILL, M., and PARKES, A. S.: Studies on ovulation. IV. Induction of ovulation in the hypophysectomized rabbit by administration of anterior lobe extracts. V. The action of the ovulation-producing substance of urine of pregnancy on the hypophysectomized rabbit, *Proc. Physiol. Soc., Jr. Physiol.*, 1931, lxxi, 36-46.
- ⁶⁰CAMPBELL, A. D., and COLLIP, J. B.: Notes on clinical use of certain placental extracts, *Canad. Med. Assoc. Jr.*, 1930, xxiii, 633-636.
- ⁶¹SEITZ, L.: Über den Einfluss der inneren Sekretion auf Entwicklung und Erkrankung der weiblichen Sexualsphäre und über Hormontherapie gynäkologischer Störungen, *Monatschr. f. Geburtsh. u. Gynäk.*, 1930, lxxxiv, 79-90.
- ⁶²HIRSCH-HOFFMANN, H. U., and WULK, H.: Weiterer Beitrag zur klinischen Verwendbarkeit des Hypophysenvorderlappenhormons ("Homhormon"), *Zentralbl. f. Gynäk.*, 1930, liv, 457-464.
- ⁶³KOEHLER, G.: Klinische Erfahrungen mit dem Hypophysenvorderlappenhormon "Prolactin", *Klin. Wchnschr.*, 1930, ix, 110-113.
- ⁶⁴EHRHARDT, K.: Klinische und tierexperimentelle Untersuchungen über Hormone des Hypophysenvorderlappens, *Arch. f. Gynäk.*, 1932, cxlviii, 235-264.
- ⁶⁵DE MAORTUA, C.: Bemerkung zur Arbeit von Prof. Dr. Esch über "Hormontherapie durch intramuskuläre Injektionen von Schwangerenblut bei Menstruationsstörungen", *Zentralbl. f. Gynäk.*, 1930, liv, 736.
- ⁶⁶ESCH, P.: Hormontherapie durch intramuskuläre Injektionen von Schwangerenblut bei Menstruationsstörungen, *Zentralbl. f. Gynäk.*, 1930, liv, 19-26.
- ⁶⁷FLUHMAN, C. F.: The influence of sex hormones on the reticulo-endothelial cells of the uterus, *Am. Jr. Obst. and Gynec.*, 1932, xxiv, 654-667.
- ⁶⁸MARTIN, E.: Die hemmende Wirkung des Prolactin, *Deutsch. med. Wchnschr.*, 1930, lvi, 580-581.
- ⁶⁹NOVAK, E., and HURD, G. B.: Use of anterior pituitary luteinizing substance in treatment of functional uterine bleeding, *Am. Jr. Obst. and Gynec.*, 1931, xxii, 501-512.
- ⁷⁰SIEBKE, H.: Thyelkinin und Androkinin, das weibliche und männliche Sexualhormon, im Körper der Frau, *Arch. f. Gynäk.*, 1931, cxlvi, 417-462.

Animal Experiments with Adrenal Cortical Extracts*†

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SINCE the extraction of a potent principle from the adrenal cortex by Swingle and Pfiffner¹⁰ and by Hartmann⁸ much greater interest has centered upon this gland than ever before. Animal experimentation has at last acquired a tool to work with, and it is being used extensively. Great hopes have been entertained for the successful treatment of Addison's disease, and the cortical extract has been used for this purpose with some degree of success by Rowntree and others.¹⁰ The very nature of this condition, however, would preclude the possibility of a cure, since it is caused in most cases by a progressive, destructive lesion of the adrenal glands. The only hope therefore is that cortical extract can replace the normal secretion. This would mean lifelong treatment, though in rare instances of tuberculosis of the glands, it might be that treatment would be necessary only through a critical period of greatest adrenal insufficiency and could be discontinued if the disease in the glands became arrested. Examples of cured

or healed tuberculosis of the adrenals, however, must be very rare.

One is reminded of the discovery of insulin, and the optimism which prevailed as to the cure of diabetes; but in spite of insulin, the mortality from this disease is greater than ever.¹⁴ Also, the failure of Collip's parathormone to replace completely the secretion of the parathyroid glands has been reported by Lisser and Shepardson.¹⁰ Because of these recent experiences, adrenal cortical extract has probably not excited clinicians as much as it has those working in the field of experimental biology. For the present, its biological significance far outweighs the possibility of its clinical application.

Even before a cortical extract was available, a considerable amount of knowledge had been assembled through clinical observation and pathological study, as well as by experiments upon the effects of adrenalectomy. Briefly, lesions causing hypofunction of the cortex have been associated with: (1) pseudohermaphroditism in the newborn; (2) a questionable failure of development of the central nervous system in anencephaly (probably coincidental); (3) hyperplasia of the

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thyroid²¹; (4) Addison's disease; (5) myasthenia gravis.

Lesions which cause hyperfunction of the adrenals (hyperplasia, adenomas, functioning carcinomas) are associated with, or may cause: (1) precocious puberty; (2) so-called adrenal virilism, masculinism, or a condition of pseudohermaphroditism in the adult female; less well-defined sexual changes (as gynecomastia) in the adult male. This list omits, of course, all conditions which have been attributed to malfunction of the adrenal medulla.

It is these physical and sexual changes which have interested us most. The adrenal cortex is so intimately bound up with, not only the phenomenon of reproduction, but the physical configuration of the body, that these aspects seem to be of much greater biological significance (and probably, in the future, of greater practical significance) than the more dramatic, but much more rare disease called Addison's disease. We have, therefore, confined our studies to a few of the thyroid and sexual phases now susceptible of investigation. Rats were used advisedly, despite the impression that the adrenals cannot be removed completely from these animals. Pencharz, Olmstead and Giragossintz¹⁵ and Freed, Brownfield, and Evans⁶ have shown that when a careful operation is performed, all rats die in from five to eight days. Carr, in this work, has had an average mortality of 88 per cent in less than eight days. In those rats which did not develop signs of acute insufficiency in six days, it was concluded that the operation had not been complete, and the animals discarded, unless the experiment called

for animals in a state of chronic insufficiency. It is not our purpose in this paper to detail the large number of animal experiments which have been made, but rather, by citing some of the results, to point out the trend of adrenal gland investigations, and to show how these, in time, will undoubtedly clear up many clinical problems. Biological research can no more be divorced from clinical medicine than can mathematics from astronomy.

The connection between the adrenal glands and the gonads is obvious in spite of many apparent contradictions. The production of precocious puberty and the neutralization of the sex glands after puberty by hyperfunction of the adrenal cortex presents a seeming paradox. One case of masculinism reported by Gibson,⁷ and seen by us, had the hirsutism and enlarged clitoris of adrenal virilism (she had a large adrenal tumor at operation), but while presenting these masculine features, she also had definite hyperplasia of the endometrium exactly similar to the decidual reaction of pregnancy. Corey and Britton⁵ have reported a change in the ovaries and testes of rats following the administration of Swingle and Pfiffner's extract which they interpret as evidence of precocious puberty, and Connor³ has reported degeneration of the ovaries of chickens following injections of a watery extract of adrenal cortex. Müller¹² likewise produced regressive changes of the sexual apparatus of rats. We were able⁴ to stop the estrus cycle of mature rats by injections of watery extracts of adrenal cortex, but, using an extract prepared by us after Swingle and Pfiffner's method, we

could not confirm Corey and Britton's results as to precocious puberty. It is nevertheless obvious that at least some of the sexual changes which have been found clinically have been reproduced experimentally, and that certainly progress towards the solution of these problems may be reported.

The retrograde sexual changes in adrenal insufficiency were first noted in a series of eighty normal animals. Following the estrus cycles of mature female white rats by vaginal smear we found that the normal sexual rhythm stopped following adrenalectomy. Autopsy findings in these animals showed a consistent and early degeneration of the corpora lutea of menstruation. It was this association that led Vincent²⁰ to suggest that the corpora lutea acted as accessory adrenal cortices, and by this mechanism Stewart and Rogoff¹⁸ explained the longer postoperative survival period of pregnant dogs. The corpora lutea of rats are constantly present in the rat ovary as bodies of menstruation, lactation, or pregnancy. We were able to observe the same degeneration of the corpora lutea in three biological stages, that is not only during the estrus cycle but also in the ovaries of either lactating or pregnant animals after adrenalectomy. Similarly, subsequent to the degeneration, lactation ceased and if occurring on or before the sixteenth day of gestation, pregnancy was interrupted. The corpora lutea are not essential in pregnancy after the seventeenth or eighteenth day of gestation, and although after this period the same degeneration of the corpora lutea was noted, the animals went on to term, either delivering without lactation and

dying a few days after parturition or dying in labor from asthenia and uterine inertia with the young stuck in the birth canal. It would seem then that these retrograde changes in adrenal insufficiency work by a secondary mechanism through the corpora lutea which degenerate, interrupting all normal sexual processes.

With an extract made after the manner of Swingle and Pfiffner, and known, through constant assay on adrenalectomized rats to contain the viable principle described by them, we attempted to prevent this degenerative change. With this extract we were unable to do so. The corpus luteum degeneration with inhibited estrus, or lack of lactation and abortion in the pregnant animal, continued as usual. In fact the degenerative changes were more marked in several injected cases than in those animals with untreated adrenal insufficiency. In the male, loss of libido and potency were noted due to degeneration of the cells of the seminiferous tubules. Here again a cortical extract known to contain the viable principle was ineffective in maintaining potency and preventing this degenerative change. It seemed to hasten rather than to retard it.

To study Vincent's theory that the sex glands contribute a substance to augment or replace cortical secretion, the postoperative survival period of adrenalectomized animals with and without the gonads was taken. Both in males and females the animals without gonads lived longer than those with, although cortical extract would keep either class alive indefinitely.

For many years Warthin²¹ insisted that Graves' disease was a constitu-

tional disease of which hyperplasia of the thyroid was only a part. He called attention to the presence also of hyperplasia of the thymus and lymphoid apparatus and hypofunction of the adrenal glands. Experimental evidence has been accumulating that part, if not all, of this anatomical complex can be produced by causing adrenal insufficiency. Jaffe⁹ noted hypertrophy of the thymus in adrenalectomized animals. Marine, Manley, and Baumann¹² observed the same thing, with also hypertrophy of the thyroid. More recently Scott and Bradford¹⁷ regularly found an enlargement of the thymus in adrenal insufficiency. We can add that animals suffering from total or partial lack of adrenal cortical secretion show definite enlargement of the thymus as well as generalized lymphoid tissue hyperplasia, and a peculiar change in the thyroid to be regarded as an hypertrophy rather than a true hyperplasia. There is a change in the staining quality of the colloid, and a prominence of the acini not found in the normal gland. A more prolonged experiment may produce more pronounced changes.

Zwemer and others have found that thyroidectomized cats live longer after adrenalectomy than normal adrenalectomized animals. If the normal adrenalectomized cats are given thyroid extract the postoperative survival period is still further shortened. We have found this mechanism operative in the rat, the animals with both adrenals and the thyroid gland removed living 35 per cent longer than adrenalectomized animals retaining the thyroid gland. If the simple adrenalectomized animal is given thyroid ex-

tract, the survival period is still further shortened. We are at present giving both thyroid and adrenal cortical extract to adrenalectomized rats to discover whether or not this antagonism, biologically suggested, exists in the chemically extracted gland substance.

These specific changes are interesting but still less important clinically than the reaction of animals with adrenal insufficiency to environment and diet. For instance, we have been able to vary the postoperative survival period of adrenalectomized animals over 100 per cent by regulations of diet alone. Certain vitamin deficiencies and a high protein diet shorten the survival period, while a high fluid intake, additions of starches and other substances, extend it. Wide daily fluctuations in temperature influence the animals badly, while a climate a degree or two above that of the body is beneficial.

We believe that the diet and other elements of general treatment are as important in maintaining the life of animals with adrenal insufficiency and of patients with Addison's disease as is the extract itself, and that while this extract does maintain life it still lacks certain components essential to a biological equilibrium.

SUMMARY

We have shown that a definite connection exists between adrenal insufficiency and such changes in the lymphoid apparatus as regeneration or hypertrophy of the thymus and hyperplasia of the lymphoid elements.

In the thyroid an increase in size accompanies adrenal insufficiency. The

removal of the thyroid gland extends the postoperative survival period of adrenalectomized animals. Those with adrenal insufficiency are killed by a dosage of thyroid extract which does not affect the normal animals.

The reproductive system responds to adrenal insufficiency by: a cessation of estrus; a softening and atrophy of the testicles; abortion or resorption of the fetuses (if the insufficiency occurs before the seventeenth day of gestation); and cessation of lactation. All of these changes apparently operate

through the secondary atrophy of the gonads.

We were unable to prevent any of these changes by administering cortical extract carrying the viable principle.

The effect of the extract in normal animals has produced a cessation of the estrus cycle of rats, and degeneration of the ovary of chickens.

Finally, cortical extracts as made by us either contain more than one principle or else we have not extracted the complete biological unit.

BIBLIOGRAPHY

- ¹CARR, J. L.: Effects of ovaries in various stages of activity and of pregnancy upon adrenalectomized rats, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxix, 128-130.
- ²CARR, J. L.: Effect of Swingle's extract upon lactation in adrenalectomized white rat, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxix, 131.
- ³CONNOR, C. L.: The effect of suprarenal cortical substance on the ovaries of chickens and on chicken tumors, *Arch. Path.*, 1930, ix, 1296.
- ⁴CONNOR, C. L.: Effects of adrenal cortical extracts upon sex organs of animals, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxix, 131-134.
- ⁵COREY, E. L., and BRITTON, S. W.: Induction of precocious sexual maturity by cortico-adrenal extract, *Am. J. Physiol.*, 1931, xcix, 33-43.
- ⁶FREED, S. C., BROWNFIELD, B., and EVAN, H. M.: Effect of adrenalectomy on testes of rat, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxix, 1-3.
- ⁷GIBSON, T. E.: Diagnosis of adrenal tumors, with classification of adrenal tumor syndromes, and report of cases, *Jr. Urol.*, 1927, xviii, 33-59.
- ⁸HARTMANN, F. A., and BROWNELL, K. A.: The hormone of the adrenal cortex, *Proc. Soc. Exper. Biol. and Med.*, 1930, xxvii, 938-939.
- ⁹JAFFE, H. L.: The influence of the suprarenal gland on the thymus. I. Regeneration of the thymus following double suprarenalectomy in the rat, *Jr. Exper. Med.*, 1924, xl, 325-342.—II. Direct evidence of regeneration of the involuted thymus following double suprarenalectomy in the rat, *ibid.*, 1924, xl, 619-625.—III. Stimulation of the thymus gland following double suprarenalectomy in young rats, *ibid.*, 1924, xl, 753-759.
- ¹⁰LISSER, H., and SHEPARDSON, H. C.: Further and final report on case of tetania parathyreopriva, treated for year with parathyroid extract (Collip), with eventual death and autopsy, *Endocrinology*, 1929, xiii, 427-454.
- ¹¹MARINE, D.: The present status of the functions of the thyroid gland, *Physiol. Rev.*, 1922, ii, 521-551.
- ¹²MARINE, D., MANLEY, O. T., and BAYMANN, E. J.: The influence of thyroidectomy, gonadectomy, suprarenalectomy, and splenectomy on the thymus gland of rabbits, *Jr. Exper. Med.*, 1924, xl, 429-443.
- ¹³MÜLLER, C.: Der Einfluss der Hyperinterrenalisierung auf die Entwicklung der weiblichen Geschlechtsorgane, *Endokrinologie*, 1931, viii, 5-14.
- ¹⁴PALMER, L. J.: Is insulin reducing diabetic mortality? Conclusions from study of diabetic deaths in Washington in 1929, *Northwest Med.*, 1931, xxx, 311-322.
- ¹⁵PENCHARZ, R. L., OLMSFAD, J. M. D., and

- GIRAGOSSINTZ, G.: Results of total and partial adrenalectomy and adrenal transplantation in the albino rat, *Science*, 1930, lxxii, 175-176.
- ¹⁶ROWNTREE, L. G., and others: Treatment of Addison's disease with cortical hormone of suprarenal gland; summary of immediate results in twenty cases treated with preparation made by Swingle and Pfiffner, Jr. *Am. Med. Assoc.*, 1931, xcvi, 1446-1453.
- ¹⁷SCOTT, W. J. M., and BRADFORD, W. L.: Effect of adrenal cortex upon thymic weight and resistance to bacterial intoxication in chronic adrenal insufficiency, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 428-431.
- ¹⁸STEWART, G. N., and ROGOFF, J. M.: Studies on adrenal insufficiency; influence of pregnancy upon survival period in adrenalectomized dogs, *Am. Jr. Physiol.*, 1927, lxxix, 508-535.
- ¹⁹SWINGLE, W. W., and PFIFFNER, J. J.: Studies on adrenal cortex; effect of lipid fraction upon life-span of adrenalectomized cats; *Am. Jr. Physiol.*, 1931, xcvi, 153-163.—Studies on adrenal cortex; aqueous extract of adrenal cortex which maintains life of bilaterally adrenalectomized cats, *ibid.*, xcvi, 164-179.
- ²⁰BRITTON, S. W.: Adrenal insufficiency and related considerations, *Physiol. Rev.*, 1930, x, 629-630. (Quotation from VINCENT, S.: *Internal secretion and the ductless glands*, 1924, Edward Arnold & Co., London).
- ²¹WARTHIN, A. S.: Constitutional entity of exophthalmic goiter and so-called toxic adenoma, *ANN. INT. MED.*, 1928, ii, 553-570.

Editorials

"MEDICAL CARE FOR THE AMERICAN PEOPLE"

At a meeting of the Board of Regents of the American College of Physicians on February 7, 1933, the Committee on Public Relations offered a report on the final publication of the Committee on the Costs of Medical Care, entitled "Medical Care for the American People." By a resolution, the Board of Regents approved the report of the Committee on Public Relations and directed that it be printed in the ANNALS OF INTERNAL MEDICINE.

REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

The final report of the Committee on the Costs of Medical Care is entitled: "Medical Care for the American People."

It is the twenty-eighth publication of a series representing an extensive and intensive effort to collect the factual data concerning numerous problems involved. These studies were made over a period of five years, with the expenditure of an extraordinary amount of thought, effort, and money.

The facts presented are of immense importance to the country as a whole and the medical profession in particular. They deserve the most careful study and consideration.

The detailed information is contained in the twenty-seven interim reports previously published, and only

a brief summary is included in the final report. The main emphasis of the final report is placed upon certain definite recommendations proposed by the Committee as the basis for a plan of reorganization of medical practice, so as to meet the social and economic defects of the existing system brought out by the factual data.

These recommendations are in the form of separate majority and minority reports with a few members of the Committee declining to assent to either report.

The widespread discussion which has followed the publication of the final report is centered upon the recommendations suggested. This is most unfortunate as it has overshadowed the great value and significance of the studies upon which these recommendations are presumably based.

It is the opinion of your Committee that the publication of definite recommendations was premature and unjustified by the facts presented. A careful analysis of the text of the reports shows that the recommendations are really only tentative suggestions for future consideration and careful experimentation, and in our opinion should have been offered as such.

It is also our belief that the actual factual data contained in the various reports are of such value that they deserve most careful study on the part of the medical profession. These facts reveal a situation which calls for con-

sideration and action leading to modification of existing medical practice, and in any such modification the medical profession should take a leading part.

It would be very unfortunate if prejudice caused by differences of opinion concerning the recommendations should belittle the value of the facts themselves. It would be still more unfortunate if either prejudice or inaction should deprive the medical profession of its rightful position of leadership in any program for remedying existing inequalities or injustices in the operation of the practice of preventive and curative medicine.

Our Committee, therefore, recommends that the individual Fellows of the American College of Physicians be urged to study the facts presented in the report of the Committee on the Costs of Medical Care, uninfluenced by the acrimonious discussion which has been raised by the publication of the various recommendations; and we also recommend that the organized representatives of the medical profession in each community be urged to consider these problems in the light of their varying local needs and conditions, for it is our belief that by this method the enlightened leadership of the medical profession can point the way to improvements of great value, both to the public and to the medical profession itself.

THE NATIONAL BOARD OF MEDICAL EXAMINERS

Examinations and the testing of knowledge have ever been an essential part of medical training. The extraordinary development of medical knowl-

edge within the last three decades has had a bewildering effect on the entire problem, and it seems almost as if we have outrun our educational system framed in simpler days and under simpler conditions.

Osler once remarked that examinations may be the best or the worst of an education. He further stated that they can be very helpful if an integral part of the training, but have been known to be the intellectual ruin of many good men.

The multiplicity of examinations, college, hospital, and licensure, with the general lack of uniformity, emphasized the need of a central qualifying body such as the National Board of Medical Examiners. It was organized in 1915 and the first examination was held in October 1916. During the first six years the examination included written and practical tests in the six fundamental sciences and four clinical branches and lasted for a period of seven days.

In 1922 the examination was divided into three parts, the first, which is taken after the completion of two or more years of the medical school course, being a written test in the six pre-clinical sciences: anatomy, biochemistry, physiology, pathology, bacteriology, and pharmacology. The second written test includes the four clinical branches, medicine, surgery, obstetrics and gynecology, and public health, and is taken at the completion of four years of study. Part three is taken only after one year of satisfactory hospital interne service.

This examination comprises: clinical surgery, including applied anatomy, surgical pathology, and the surgical

and head specialties; clinical medicine, including neurology, pediatrics and dermatology, clinical laboratory, medical pathology and applied physiology, biochemistry, pharmacology, and roentgenology; obstetrics and gynecology, and public health (which also includes applied bacteriology).

The written tests are conducted on the proctor plan and are held in the different medical college centers in the United States and Canada. The practical and clinical part three examination is conducted at twenty centers in different sections of the country. At each of these centers a subsidiary board of examiners has been organized, under whose supervision the examination is conducted.

The membership has been gradually increased from the original fifteen members to the present membership of twenty-seven, representing the three federal medical services, the Association of American Medical Colleges, the Council on Medical Education of the American Medical Association, the Federation of State Medical Boards, and twelve members from the profession at large, selected with special reference to their geographical distribution. To prevent "life membership" and to ensure the frequent election of new members, the Constitution provides that, with the exception of the members from the Federal services, each member is elected for a term of six years and can succeed himself for one additional term only.

By continuous and intensive study a comprehensive examination has been developed in keeping with the highest medical training now prevailing in American medical schools. Successful

candidates are granted a certificate as a Diplomate of the National Board, and are permitted to use the letters D.N.B. after their names. They are so designated in the Directory issued by the American Medical Association. This certificate has been recognized by forty-two states, being accepted in lieu of the required state medical licensure examination. It is also accepted as satisfying by the qualification boards of England, Scotland, and the Irish Free State for admission to the clinical part of the final examination for entry on the British registry.

The plan of examination has served as a model for state boards and has greatly promoted the more extensive use of the practical and clinical tests in licensure examinations. The national boards of examiners in the different specialties organized in recent years have patterned their examination largely after that of the National Board.

The adoption of the examination by a number of leading medical schools is a significant endorsement. Yale University Medical School requires all students to take and pass the National Board examinations; the answer papers are graded by National Board examiners. The students at Yale take an oral comprehensive examination at the end of their second and fourth years respectively, and unless successful in these oral and practical examinations, they are not eligible for the National Board examinations.

Beginning this year Duke University requires all its students to take the National Board examination. The answer papers are held for three days, examined by the Faculty for their own purposes and records, then forwarded

to the National Board's office where they are graded in the usual way. The same plan prevails at the College of Medical Evangelists, Los Angeles, where all students are required to take the National Board examination.

At the University of Minnesota the students have the choice of taking either the National Board's written examination, or the Medical College comprehensives at the end of their second and fourth years. The papers are first graded by the Medical Faculty and then forwarded to the National Board office.

Georgetown University has announced that beginning next year it will require all students to take the National Board examination. The plan is also being considered by the University Medical Schools of Iowa, Illinois, Columbia, Colorado, Buffalo, and Washington (St. Louis), as well as several of the two-year schools.

It is interesting to note that each year a considerable number of candidates are completing their National Board examinations, after having secured their medical license, which indicates that it is steadily gaining recognition as an honors examination.

By influencing the present tendencies of medical education, unifying examination procedure, and developing a comprehensive qualifying test to determine fitness to practise, the National Board is to a certain extent fulfilling its purpose and destiny.

WALTER L. BIERRING, M.D.

SPOTTED FEVER IN THE EASTERN STATES

The identification in the rural districts of the southeastern states of a

form of Rocky Mountain spotted fever was reported by Rumreich, Dyer, and Badger in 1931. In several papers in the Public Health Reports of that year^{1,2,3} they published the evidence on which the identification was based. A clinical study was made of fifty cases of a spotted fever occurring during the tick season in rural districts of Delaware, Maryland, Pennsylvania, Virginia, North Carolina, and the District of Columbia. These cases were compared with fifty urban cases of typical endemic typhus occurring in Baltimore, Savannah, Tampa, and in smaller urban communities in Georgia and Florida. Suggestive clinical differences were found between the two groups of cases. The rural group showed evidence of a more severe infection by greater prostration, higher fever, and a faster pulse. The rash in the typhus group appeared first on the trunk, was less marked on the forearms, and rarely involved the palms. In the rural cases, however, the rash appeared first about the wrists and ankles, usually involved the palms and soles, spread rapidly over the whole

¹DYER, R. E., RUMREICH, A., and BADGER, L. F.: Typhus fever; a virus of the typhus type derived from fleas collected from wild rats, Pub. Health Rep., 1931, xlvii, 334-338.

²RUMREICH, A., DYER, R. E., and BADGER, L. F.: The typhus-Rocky Mountain spotted fever group; an epidemiological and clinical study in the eastern and southeastern states, Pub. Health Rep., 1931, xlvii, 470-480.

³DYER, R. E., BADGER, L. F., and RUMREICH, A.: Rocky Mountain spotted fever (eastern type); transmission by the American dog tick (*Dermacentor variabilis*), Pub. Health Rep., 1931, xlvii, 1403-1413.

trunk, and frequently became purpuric and confluent.

Disturbances of the central nervous system of a severe order, such as meningismus, clonic twitching, and coma, were more common in the rural group. The death rate in this rural group was 14 per cent, while there were no fatalities among the fifty cases of endemic typhus. The duration of the disease in the endemic typhus group was from eleven to sixteen days, with twenty-eight of the cases terminating on the fourteenth day. Over half of the rural cases, however, persisted to between the seventeenth and the twenty-second day. It was felt by the authors that the disease in the rural group of cases did not correspond to the clinical picture of endemic typhus but resembled the spotted fever of the Rocky Mountains more closely than it did any other disease. This suggestive clinical differentiation was supported by epidemiologic data showing that in addition to the distinguishing feature of urban, as opposed to rural, residence the typhus group gave a history in thirty-nine cases of association with rats and presumably rat fleas, whereas in the rural group rodent infestation of patients' homes was determined in only seven cases. Twenty-four of these rural cases, however, gave a history of tick bite within three weeks prior to the onset, and three more of the patients had crushed engorged ticks removed from dogs. All had lived in tick-infested localities.

Blood from three cases of the rural type was injected into guinea pigs that proved susceptible, and strains of virus were perpetuated through many generations of these animals by transfers.

The lesions of the disease in guinea pigs were found in general to be similar to those caused by the Rocky Mountain spotted fever virus. Guinea pigs which had recovered were found to be still susceptible to the virus of endemic typhus and of European epidemic typhus but to be unaffected by inoculation with the virus of Rocky Mountain spotted fever.

An account of the gross and microscopic pathology of the eastern type of Rocky Mountain spotted fever, based on a study of five autopsies, has been presented in an article by Lillie.⁴ In general the lesions found were similar in character, if not always in degree of severity, to those described in the twenty-one reported autopsies of Rocky Mountain spotted fever. In such small series minor variations might well be expected. It would seem, however, that in the eastern type focal brain lesions of vascular degenerative, proliferative, and focal gliotic character were more frequent than in the western form of the disease. These brain lesions were apparently closely similar to those described in European typhus. Lillie mentions the finding of "cell inclusions resembling rickettsiae in the endothelia and walls of small vessels". A more definite identification of rickettsiae in the human tissues is reported by Pinkerton and Maxcy⁵ in connection with their study of a fatal case which at the time was

⁴LILLIE, R. D.: Pathology of the eastern type of Rocky Mountain spotted fever, Pub. Health Rep., 1931, xlv, 2840-2859.

⁵PINKERTON, H., and MAXCY, K. F.: Pathological study of a case of endemic typhus in Virginia with demonstration of *Rickettsia*, Am. Jr. Path., 1931, vii, 95.

thought to be one of endemic typhus, but which Maxcy now believes to have been spotted fever. More recently the identification of rickettsiae in the tissues of three cases of spotted fever has been reported by Pincoffs and Shaw.⁶

The occurrence of spotted fever on the eastern coast is therefore established by clinical epidemiological, immunological, and pathological data. Our knowledge, however, of the occurrence of the virus in nature in this eastern territory is still entirely fragmentary. It has been shown that the American dog tick (*Dermacentor variabilis*), which is the most common man-biting tick in most of the known infected area, can transmit the virus from guinea pig to guinea pig and that the virus in the tick persists through at least one moult. The importance of this species of tick as a vector of the disease in the east is further established by the finding, in an infested area, of dog ticks which were proven to be infectious by animal inoculation.⁷ Further extensive studies of the other

eastern ticks that may be possible vectors, and of the susceptibility of eastern rodents and small mammals which may serve as hosts, will no doubt be carried out to bring our knowledge of the maintenance of the eastern virus in nature at least abreast of what is known concerning the western virus of this disease.

It cannot readily be determined whether we are witnessing the appearance of spotted fever in the east or merely its discovery. The striking clinical characteristics of the disease favor the presumption that it could not have gone unrecognized as a clinical entity for many years. The heavy tick infestation of the southeastern states and the relatively dense human population in the same area make of all this region a potentially more important focus of the disease than the sparsely settled mountain states. That there are as yet unknown factors which affect the extension of the disease is shown, however, by the well known example of the situation in the Bitter Root valley. In this region spotted fever in humans has been known on the western side of the valley for over thirty years but has not yet spread to the eastern side, though the wood tick which transmits the virus and the rodents which serve as hosts are present on both sides. Study of this disease in the east may disclose similar instances of geographic limitation.

⁶PINCOFFS, M. C., and SHAW, C. C.: The eastern type of Rocky Mountain spotted fever; report of a case with demonstration of rickettsiae, Medical Clinics of North America, March, 1933. (In press)

⁷BADGER, L. F.: Rocky Mountain spotted fever (eastern type); virus recovered from the dog tick *Dermacentor variabilis* found in nature, Pub. Health Rep., 1932, xlvii, 2365-2369.

in science, whose interests in the developments of physical chemistry are secondary.

The subjects discussed are: The Methods of Science, Atomic Structure, Transmutation of the Elements, Valence, Radiations on Chemical Systems, New Elements and New Uses for Old Ones, and the Elixir of Life.

The first chapter, "Methods of Science", embraces many of the fields of the biological and physical sciences. The interrelationship of the development of each is emphasized. Although the treatment of each subject is superficial, owing to the nature of the volume, much striking philosophy has been included. Thus under psychology one reads, "The function of philosophy is to integrate all branches of science and form from them a closely interrelated whole."

The chapter on the "Elixir of Life" should be found interesting by medical readers. Herein the history of the futile search by the chemist for the "Elixir of Life" is reviewed. The rise of iatrochemistry, the work of Pasteur, the major conquests in the field of bacteriology and the advance of chemotherapy are developed. The sociological and international difficulties involved in the control of communicable disease are discussed.

In the introduction the authors mention that the writing of this volume was suggested by the late Dr. E. E. Slosson. In the book the spirit of Slosson is perpetuated, lending to the volume a warmth of interest and ardor which was so characteristic of the pen of that great master in this field of literature.

J. C. K., Jr.

The History of Dermatology. By WILLIAM ALLEN PUSEY, A.M., M.D., LL.D., Professor of Dermatology Emeritus, University of Illinois; President of the American Dermatological Association and of the American Medical Association from time to time. Fabricoid Linen. 233 pages, 33 illustrations. Charles C. Thomas, Springfield, Ill. and Baltimore, Md., 1933. Price \$3.00.

Any work from the pen of William A. Pusey, the Nestor of American Dermatology, must be good, and his latest *History of Dermatology* is no exception. It is a concise, absorbing story of the growth and development of dermatology from ancient times to, and including, its present status as a branch of medicine burdened with a nomenclature fearfully and wonderfully

made. The history is written in a plain unassuming style, readable and understandable by lay and professional alike. The very close, intimate, and inseparable relation between dermatology and medicine is made evident in the introduction. Since skin lesions in many instances are simply reflections of a disturbance of the general economy, it is difficult to draw a hard and fast line between the specialty and general medicine.

The early chapters deal with the development and the observations of the ancients and their interpretation of the macroscopic appearance of lesions. Later the story is taken up by periods in the various countries, Germany, Austria, Great Britain, and the United States.

It is disappointing, however, to note that Henry Stelwagon's work in dermatology is dismissed with but a few words. His monumental work on the *Diseases of the Skin* is lauded, but there is no mention of his other writings.

The intimate association of dermatology and venereal diseases as practised in foreign countries is recognized in a graphic account of the life of Neisser, whose name is inseparably associated with the discovery of the gonococcus. Ricord, whose fame rests upon his urological contributions, is given credit for his epoch-making experiments by which he differentiated the local results of the inoculation of gonorrhoeal pus from the systemic reaction of pus originating from a primary luetic lesion.

A unique and praiseworthy contribution to the literature is an *Historical Index of Dermatology* in which is given historically a sketch of the various diseases from Acanthosis Nigricans to Zona.

The appearance of the volume is not to be overlooked. It is printed on heavy glazed paper in large readable type. The cover design and the binding of fabricoid linen are additional attractive features. The numerous illustrations and photographs are unusually well reproduced and of a kind seldom seen in historical works.

The volume should find a place not alone in the library of every dermatologist but should be read and treasured by everyone interested in the growth and development of medicine.

M. S. R.



George Morris Phipson, B.S., M.D., Philadelphia
President, 1933-1934

GEORGE MORRIS PIERSOL, B. S., M. D.,

Philadelphia

President of the AMERICAN COLLEGE OF PHYSICIANS

1933 - 1934

Born, Philadelphia, October 13, 1880; graduated, William Penn Charter School, 1898; University of Pennsylvania, B. S., 1902; University of Pennsylvania School of Medicine, M.D., 1905.

Resident Physician (1905-1906), and Chief Resident Physician (1906-1907), Hospital of the University of Pennsylvania, Philadelphia; Professor to the Professor of Anatomy (1907-1910), and Associate in Medicine (1912-1921), University of Pennsylvania School of Medicine; Physician, Episcopal Hospital, Philadelphia, 1912-1916; Professor of Medicine, Woman's Medical College of Pennsylvania, 1917-1922; Lieutenant Colonel, Medical Corps, U. S. Army, 1917-1919; Commanding Officer, U. S. Army, Base Hospital No. 20, A.E.F., 1918; Medical Consultant, Fourth Army Corps, A.E.F., 1918-1919.

Professor of Medicine and Vice Dean of Medicine, Graduate School of Medicine of the University of Pennsylvania; Physician, Graduate Hospital of the University of Pennsylvania; Physician-in-Chief, Abington Memorial Hospital, Abington; Active Consultant in Medicine, Philadelphia General Hospital; Consultant to the Preston Retreat and the Chestnut Hill Hospital; Medical Director, Bell Telephone Company of Pennsylvania; Editor, *The Cyclopedia of Medicine*; ex-Editor, *The American Journal of Medical Sciences*; author of numerous medical articles.

Member: Delta Tau Delta, Alpha Mu Pi Omega, Sigma Xi and Alpha Omega Alpha fraternities; Member and ex-President, Philadelphia County Medical Society; Member, Medical Society of the State of Pennsylvania; Fellow, American Medical Association; Member, Association of American Physicians; Member and ex-President, American Gastro-Enterological Association; Member and ex-President, American Climatological and Clinical Association; Fellow, College of Physicians of Philadelphia; Member, Philadelphia Pathological Society; Member, Philadelphia Pediatric Society.

Dr. Piersol became a Fellow of the College in 1922. From 1926 to 1932 he held the office of Secretary-General. He served on the Committee on Credentials for six years and gave unstintingly of his time to this laborious task. In spite of many other activities and heavy responsibilities he has always given freely of his energy and ability to the work of the College. He enters upon his term as President with an intimate knowledge of the College's problems and with a wide acquaintanceship and popularity among its Fellows.



JONATHAN CAMPBELL MEAKINS, M.D.C.M., LL.D. (Edin.), Montreal
President-Elect, 1933-1934

JONATHAN CAMPBELL MEAKINS, M.D.C.M., LL.D. (Edin.),
F.A.C.P., F.R.C.P. (C), F.R.C.P. (Edin.), Hon. F.R.C.S. (Edin.),
F.R.S.C., F.R.S.E.,

Montreal

President-Elect of the AMERICAN COLLEGE OF PHYSICIANS
1933 - 1934

Born, Hamilton, Ontario, May 16, 1882. Graduated, Hamilton High School; McGill University, M.D.C.M., 1904. Resident Physician, Royal Victoria Hospital, Montreal, 1904-1906; Assistant in Medicine, Johns Hopkins Hospital, 1906-1907; Resident Pathologist, Presbyterian Hospital, New York City, 1907-1909; Lecturer in Clinical Medicine, McGill University, and Assistant Physician, Royal Victoria Hospital, 1909-1913; Canadian Army Medical Corps, 1914-1918; Member, Inter-Allied Chemical Warfare Conference; Consultant Physician, Canadian Army Medical Corps, 1918-1919; Christison Professor of Therapeutics and Professor of Clinical Medicine, Edinburgh University, 1919-1924; Director of Medical Research Laboratories, Edinburgh University and Royal Infirmary, 1920-1924; Consulting Physician, Royal Maternity and Simpson Memorial Hospital, Edinburgh, 1923-1924.

Director of the Department of Medicine and Professor of Medicine, McGill University, Montreal; Director of the University Clinic, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal.

Member: The Physiological Society (Great Britain); The British Medical Association; The Canadian Medical Association; Association of American Physicians; The American Physiological Society; Society of Experimental Biology and Medicine; The Montreal Medico-Chirurgical Society; and others.

Dr. Meakins has made numerous and important contributions to the medical literature in many fields. His investigations on the pathological physiology of the respiration and the circulation are very widely known.

Dr. Meakins was elected a Fellow and a Regent of the American College of Physicians in 1928. He was appointed Chairman of the Seventeenth Annual Clinical Session in Montreal, the first meeting of the College in Canada. Under his guidance, this very successful meeting set a high standard in the excellence of arrangements and the quality of the program of clinics.

College News Notes

Dr. Henry J. John (Fellow), Cleveland, Ohio, and Dr. William D. Sansum (Fellow), Santa Barbara, California, are members of the Advisory Editorial Board of the newly established journal, *Diabetes*, which made its first appearance in November, 1932.

Major George R. Callender (Fellow), Fort Sam Houston, Texas, has been elected President of the American Society of Tropical Medicine for the year 1933.

At a dinner given in his honor at the Drake Hotel, Chicago on January 3, 1933, the Honorable René Weiller, Consul-General of France, awarded to Dr. Frank Smithies the Cross of Knight of The Legion of Honor of The French Republic in recognition of his achievements with respect to Post-Graduate Medical Education in France and in medical science.

SOCIETY FOR THE ADVANCEMENT OF GASTROENTEROLOGY

The objects of the Society are:

- (a) To unite in one organization those physicians who are engaged in the specialty of Gastroenterology.
- (b) To correlate closely the clinical and experimental work of the specialty as it is performed everywhere and to make practical application of all recent advances in this field.

- (c) To stimulate and encourage research work in every phase of Gastroenterology.
- (d) To act as a control agency through which all qualifications and all requirements relating to the specialty may be standardized.
- (e) To formulate the highest standards and principles for the practise of the specialty.
- (f) To encourage legislation and public support as related to the specialty.
- (g) To edit and publish the proceedings of the Society and all matters, papers, articles, subjects and reports considered.

OFFICERS ELECTED FOR 1933

Dr. G. Randolph Manning.....President
Dr. I. L. Ritter.....1st Vice-President
Dr. E. Katz.....2nd Vice-President
Dr. Wm. C. Jacobson.....Secretary
Dr. S. Mufson.....Treasurer
Dr. S. Weiss.....Editor-in-Chief

ADVISORY BOARD

Dr. E. L. Kellogg, Honorary President
Dr. Max Einhorn
Dr. Jacob Kaufmann
Dr. Anthony Bassler
Dr. A. F. R. Andresen

Meetings are held on the fourth Wednesday of the month.

OBITUARIES

DR. WILLIAM SYDNEY THAYER

William Sydney Thayer, Fellow of the American College of Physicians, died suddenly of heart failure on December 10, 1932.

Dr. Thayer was born into a distinguished New England family at Mil-

ton, Massachusetts, on June 23, 1864. On his maternal side he was descended from Ralph Waldo Emerson; his father, James Bradley Thayer, and a brother, Ezra Thayer, held chairs in the Law School of Harvard University. Reared in the university atmosphere of Cambridge, where he lived

after the age of ten, he never lost contact with Harvard. He was graduated from the University as Bachelor of Arts in 1885, and as Doctor of Medicine in 1889, served as Visiting Physician (pro tem) at Peter Bent Brigham Hospital in 1914, and had completed two terms, beginning 1915, as a member of the Board of Overseers of Harvard University.

Meanwhile, he had been called to Baltimore by Osler from the Massachusetts General Hospital in 1890, and for the remaining forty-two years of his life he made his home in this city. He was, successively, Assistant Resident Physician, Resident Physician, and Head of the Medical Department of the Dispensary (1898-1906) of the Johns Hopkins Hospital. He practised medicine and held the position of Professor of Clinical Medicine in Johns Hopkins University from 1905 to 1918. In June 1917, he went to Russia as a member of the Red Cross Mission, and in March 1918, entered upon active duty with the United States Army in France and was appointed Chief Consultant, Medical Services, A.E.F., in June 1918; Brigadier-General, October 1, 1918. While in France he was asked to accept the position of Professor of Medicine on the university basis at Johns Hopkins. Returning from France, he relinquished his practice and held this post together with that of Physician-in-Chief of the Johns Hopkins Hospital until 1921. He then resigned, resumed his consultation practice, and became Emeritus Professor of Medicine; he continued to teach until the day of his death.

Many honors were heaped upon him. He was President of the American

Society of Tropical Medicine (1910), President of the American Society for Clinical Investigation (1913), President of the Congress of American Physicians and Surgeons (1915), of the Association of American Physicians (1921), and of the American Medical Association (1928-1929). He held honorary degrees from Washington College, University of Edinburgh, University of Chicago, University of Paris, and McGill University. He held Honorary Membership in the Therapeutical Society of Moscow, in the Association of Physicians of Great Britain and Ireland, and in the Industrial Society of Medical Hydrology. He was Honorary Fellow of the Royal Society of Medicine of Budapest, of the Royal College of Physicians of Ireland, of the Royal Society of Tropical Medicine and Hygiene, London, of the Royal Society of Medicine, London, and of the Royal College of Physicians of Edinburgh. He was associate foreign member of the Académie de Médecine, Paris, corresponding member of the Société des Hôpitaux de Paris, of the Société des Hôpitaux de Lyon, and of the Société Royale des Sciences Médicales et Naturelles de Bruxelles. His other affiliations and honors, some of outstanding importance, are too numerous to record in full; mention must be made, however, of his appointment to Commander, Legion of Honour (1927), and of his selection as Orator at the Bright Centenary at Guy's Hospital in 1927.

Dr. Thayer married Miss Susan Chisolm Read, of Charleston, S. C. in 1901. Although in ill health during the latter years of her life, she lived until 1917, and died during her husband's

absence in Russia. No children survive.

The loss to the medical profession of the United States from the death of Dr. Thayer is great; this is especially true because of the peculiarly individual nature of his contribution. The unique quality of the man lay in the imponderables of character, of brilliant linguistic accomplishment, of personal charm, of intense loyalty to persons and institutions and ideals. Though sought on every hand for the wisdom of his clinical judgment, which was second to none, he will be remembered by those who knew him best as one who transcended medicine and became a great man.

(Furnished by JOHN T. KING, JR., M.D., F.A.C.P., Baltimore, Md.)

DR. HENRY DASPIT

Dr. Henry Daspit died December 19, 1932, as a result of influenza-bronchopneumonia. He had been sick but a few days and was rapidly overwhelmed by the severity of the infection.

Dr. Daspit graduated from Tulane University in 1907 and promptly obtained a position in the Louisiana State Hospital for the Insane, at Jackson, which led to his subsequent interest in neuropsychiatry, in which he specialized thereafter. On his return to New Orleans from Jackson he served in various ranks in the Department of Nervous and Mental Diseases of Tulane Medical School, obtaining in 1921 the Professorship of Neurology and, in 1926 when the chair of Psychiatry was combined with that of Neurology, he held this twofold po-

sition. In 1928 he became Dean of the Graduate School. In addition to these two positions, at the time of his death he was a senior visiting physician at Charity Hospital, superintendent of the City Hospital for Mental Diseases and City Alienist; he was consultant in Neurology for the United States Marine Hospital No. 14 and held a similar position in some four or five other hospitals. His interest was not confined solely to his specialty and to his pedagogic activities. He was a public-minded citizen and a goodly portion of his time was occupied with many sociologic and hygienic activities.

A member of an old French family, Dr. Daspit happily combined attributes of friendliness, charm and sociability, so that he had a host of friends as well as innumerable acquaintances. Clear thinking, kindly and always willing to help others, his advice and assistance were sought by many.

He was well known in Louisiana, Mississippi, Alabama, and Texas through his contact with the undergraduate students and the graduate students of the Medical School of Tulane University. His death came as a shock to the many who had been taught by him and who have always known him as a keen, physically active, and industrious teacher.

In 1927 he became a Fellow in the American College of Physicians and was interested intensely in its activities and its program. He did much to further the purposes of the organization and was enthusiastic in his belief in what could be accomplished by it.

(Furnished by J. H. MUSSLER, M.D., F.A.C.P., New Orleans, La.)

DR. FENTON BENEDICT TURCK

Dr. Fenton Benedict Turck (Associate), New York City, died November 16, 1932, of angina pectoris; aged seventy-five years.

Dr. Turck received his medical degree from the Northwestern University Medical School in 1891. He did postgraduate work at the Pathological Institute of Berlin. He was House Surgeon in the Alexian Brothers Hospital, Chicago, 1891-92; Instructor in Internal Medicine at the Postgraduate Medical School, Chicago, 1893; Lecturer, Jefferson Medical College of Philadelphia, 1896; Lecturer, University of Rome, Italy, 1906; and the Founder and Director of the Laboratory, Turck Foundation, at the time of his death.

Dr. Turck was the author of 102 articles published in the United States and Europe. During the World War, he held the rank of Captain in the Medical Corps of the U. S. Army. He was a member of King's County Medical Society, the New York State Medical Association, the American Association for Advancement of Science, the Association for the Study of Internal Secretions, the Royal Geographic Society (Lisbon), Société d'Urologie de France, and a Fellow of the American Medical Association and of the New York Academy of Medicine. He had been an Associate of the American College of Physicians for many years.

DR. ALFRED HENRY

Dr. Alfred Henry (Associate), Indianapolis, Indiana, died suddenly De-

cember 12, 1932, of angina pectoris; aged fifty-seven years.

Dr. Henry graduated from the Indiana Medical College, School of Medicine of Purdue University, Indianapolis, in 1907. He did postgraduate work at the Trudeau Sanatorium and at Bellevue Hospital of New York City. From 1914 to 1920, he was Professor of Anatomy, Normal College of Gymnastic Union; from 1916 to 1921, Professor of Physiology, Indiana Dental College; and since 1912, he had occupied various teaching positions on the staff of the Indiana University School of Medicine, being Clinical Professor of Medicine at the time of his death.

In 1911, Dr. Henry aided in the organization of the Marion County Tuberculosis Association, becoming its first president and serving in that capacity until 1927, when he retired. He was prominent in state anti-tuberculosis activities and was elected President of the Indiana Tuberculosis Association in 1917. He was a director of the Indianapolis free tuberculosis clinics from 1911 to the time of his death. In 1916, he was president of the Mississippi Valley Conference for Tuberculosis Workers. He was president of the National Tuberculosis Association for the year 1931-32.

Some of Dr. Henry's additional appointments included: President of Board of Directors, Sunnyside Sanatorium, Oaklandon; Member of Staff, St. Vincent's Methodist Hospital, Robert W. Long Hospital and the James Whitcomb Riley Hospital for Children. He had been an Associate of the American College of Physicians since 1921.

absence in Russia. No children survive.

The loss to the medical profession of the United States from the death of Dr. Thayer is great; this is especially true because of the peculiarly individual nature of his contribution. The unique quality of the man lay in the imponderables of character, of brilliant linguistic accomplishment, of personal charm, of intense loyalty to persons and institutions and ideals. Though sought on every hand for the wisdom of his clinical judgment, which was second to none, he will be remembered by those who knew him best as one who transcended medicine and became a great man.

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DR. HENRY DASPIT

Dr. Henry Daspit died December 19, 1932, as a result of influenza-bronchopneumonia. He had been sick but a few days and was rapidly overwhelmed by the severity of the infection.

Dr. Daspit graduated from Tulane University in 1907 and promptly obtained a position in the Louisiana State Hospital for the Insane, at Jackson, which led to his subsequent interest in neuropsychiatry, in which he specialized thereafter. On his return to New Orleans from Jackson he served in various ranks in the Department of Nervous and Mental Diseases of Tulane Medical School, obtaining in 1921 the Professorship of Neurology and, in 1926 when the chair of Psychiatry was combined with that of Neurology, he held this twofold po-

sition. In 1928 he became Dean of the Graduate School. In addition to these two positions, at the time of his death he was a senior visiting physician at Charity Hospital, superintendent of the City Hospital for Mental Diseases and City Alienist; he was consultant in Neurology for the United States Marine Hospital No. 14 and held a similar position in some four or five other hospitals. His interest was not confined solely to his specialty and to his pedagogic activities. He was a public-minded citizen and a goodly portion of his time was occupied with many sociologic and hygienic activities.

A member of an old French family, Dr. Daspit happily combined attributes of friendliness, charm and sociability, so that he had a host of friends as well as innumerable acquaintances. Clear thinking, kindly and always willing to help others, his advice and assistance were sought by many.

He was well known in Louisiana, Mississippi, Alabama, and Texas through his contact with the undergraduate students and the graduate students of the Medical School of Tulane University. His death came as a shock to the many who had been taught by him and who have always known him as a keen, physically active, and industrious teacher.

In 1927 he became a Fellow in the American College of Physicians and was interested intensely in its activities and its program. He did much to further the purposes of the organization and was enthusiastic in his belief in what could be accomplished by it.

(Furnished by J. H. MURPHY, M.D., F.A.C.P., New Orleans, La.)

DR. FENTON BENEDICT TURCK

Dr. Fenton Benedict Turck (Associate), New York City, died November 16, 1932, of angina pectoris; aged seventy-five years.

Dr. Turck received his medical degree from the Northwestern University Medical School in 1891. He did postgraduate work at the Pathological Institute of Berlin. He was House Surgeon in the Alexian Brothers Hospital, Chicago, 1891-92; Instructor in Internal Medicine at the Postgraduate Medical School, Chicago, 1893; Lecturer, Jefferson Medical College of Philadelphia, 1896; Lecturer, University of Rome, Italy, 1906; and the Founder and Director of the Laboratory, Turck Foundation, at the time of his death.

Dr. Turck was the author of 102 articles published in the United States and Europe. During the World War, he held the rank of Captain in the Medical Corps of the U. S. Army. He was a member of King's County Medical Society, the New York State Medical Association, the American Association for Advancement of Science, the Association for the Study of Internal Secretions, the Royal Geographic Society (Lisbon), Société d'Urologie de France, and a Fellow of the American Medical Association and of the New York Academy of Medicine. He had been an Associate of the American College of Physicians for many years.

DR. ALFRED HENRY

Dr. Alfred Henry (Associate), Indianapolis, Indiana, died suddenly De-

cember 12, 1932, of angina pectoris; aged fifty-seven years.

Dr. Henry graduated from the Indiana Medical College, School of Medicine of Purdue University, Indianapolis, in 1907. He did postgraduate work at the Trudeau Sanatorium and at Bellevue Hospital of New York City. From 1914 to 1920, he was Professor of Anatomy, Normal College of Gymnastic Union; from 1916 to 1921, Professor of Physiology, Indiana Dental College; and since 1912, he had occupied various teaching positions on the staff of the Indiana University School of Medicine, being Clinical Professor of Medicine at the time of his death.

In 1911, Dr. Henry aided in the organization of the Marion County Tuberculosis Association, becoming its first president and serving in that capacity until 1927, when he retired. He was prominent in state anti-tuberculosis activities and was elected President of the Indiana Tuberculosis Association in 1917. He was a director of the Indianapolis free tuberculosis clinics from 1911 to the time of his death. In 1916, he was president of the Mississippi Valley Conference for Tuberculosis Workers. He was president of the National Tuberculosis Association for the year 1931-32.

Some of Dr. Henry's additional appointments included: President of Board of Directors, Sunnyside Sanatorium, Oaklandon; Member of Staff, St. Vincent's Methodist Hospital, Robert W. Long Hospital and the James Whitcomb Riley Hospital for Children. He had been an Associate of the American College of Physicians since 1921.

DR. GAYFREE ELLISON

Dr. Gayfree Ellison, Norman, Oklahoma, died December 22, 1932. He was born in 1875 and received his A.B. degree from Bethany College, Lindsborg, Kansas. He served in the Spanish-American War with the 7th Kansas Infantry under General Fred Funston, and took part in the pursuit and capture of Aguinaldo.

He received his M.D. degree from Rush Medical College in 1903; interned, Augustina Hospital, 1903-1904; assistant to Dr. A. J. Ochsner, 1904-1906; practised at Muskegon, Michigan, 1906-1908; practised at Oklahoma City, 1908-1911; Bacteriologist, Oklahoma State Board of Health, 1911-1914; Professor of Bacteriology, Medical School of University of Oklahoma, 1914-1928; World War, medical service, 1917-1919; Professor of Epidemiology and Public Health, 1928 to time of death. He was also school physician in charge of student health in the University of Oklahoma from 1928 until the time of death.

Dr. Ellison was a member of Cleveland County Medical Society, Oklahoma City Academy of Medicine, Oklahoma State Medical Association, American Medical Association, Southern Medical Association, Society of American Bacteriologists, and a Fellow of the American College of Physicians.

Dr. Ellison left a wife, a son, Gayfree, and a daughter, Helena. He was a man of exceedingly high principles, a student, and had the highest ideals of medicine. He had always taken an active part in the betterment of the medical profession in his local, state and national affairs.

(Furnished by LEA A. RIELY, M.D., F.A.C.P., Governor for Oklahoma.)

DR. EDWARD LOUIS HEINTZ

Dr. Edward Louis Heintz (Fellow), Chicago, Ill., died suddenly December 7, 1932, of heart disease; age fifty-eight years.

Dr. Heintz was born in Rolla, Mo., April 27, 1874. He attended the University of South Dakota from 1891 to 1893, which institution honored him in 1922 with an LL.D. degree. He graduated from the St. Louis College of Pharmacy in 1898, with the degree of Ph.G., and from the University of Illinois College of Medicine, 1901, with the degree of M.D. For many years he occupied the chair of Assistant Professor of Medicine and Clinical Medicine at the University of Illinois College of Medicine, having retired to emeritus rank at the time of his death. Dr. Heintz was Attending Physician to the University Hospital, and Secretary of the University Hospital School of Nursing. He was a member of the Illinois State Medical Society, the Chicago Medical Society, the Research Club of the University of Illinois College of Medicine and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1919.

Dr. Heintz was also active in civic and public affairs, being Chairman of a Chamber of Commerce Committee, working toward the development of a large park around the west side schools and hospitals. He was a member, and for over thirty years a Grand Officer, of the Alpha Kappa Kappa Fraternity.

**DR. FREDERICK TREMAINE
BILLINGS**

Dr. Frederick Tremaine Billings (Fellow), Pittsburgh, Pa., died January 5, 1933; aged fifty-nine years.

Dr. Billings was born at Ridgewood, N. J., attended Public Schools in Washington, D. C., the Lake Mohican Military Academy and the United States Naval Academy at Annapolis, Maryland. He received his medical training at Yale University, graduating in 1898. Dr. Billings interned at Patterson (N. J.) General Hospital, and in 1922 became chief examiner of the Equitable Life Assurance Society, whereupon he went to Pittsburgh.

Dr. Billings served on the staffs of several Pittsburgh Hospitals including the Allegheny General, St. Joseph's, St. Francis, Western Pennsylvania, Presbyterian and Southside Hospitals. At one time he was chief of the University of Pittsburgh Medical Dispensary and was an instructor in Internal Medicine in that institution. During the World War he held the rank of Lieutenant Commander in the Medical Corps of the U. S. Navy (Reserve Forces).

Dr. Billings was a member of the Allegheny County Medical Society, the Pennsylvania State Medical Society, the Pittsburgh Academy of Medicine, the Central States Pediatric Society and of the American Medical Association. He had been a Fellow of the American College of Physicians since 1919.

(Furnished by E. BOSWORTH MCCREADY, M.D., F.A.C.P., Governor for Western Pennsylvania.)

**DR. FRANK HARTON
PRATTEN**

Dr. Frank Harton Pratten (Fellow) London, Ontario, although suffering with hypertension for the past year, died rather unexpectedly December 10, 1932; aged forty-six.

Dr. Pratten was born in Waterford, Ontario, obtained his elementary education in Ontario and graduated in medicine from the University of Toronto in 1911. He was Resident Physician of Muskoka Hospital for Consumptives at Gravenhurst from then until 1914, when he became a member of the staff of the Toronto General Hospital, remaining there until he went overseas in 1915. He was in charge of the chest wards at Moore Barracks' Hospital for some time, following which he served with a front line unit in France, taking part in the historic engagement of Vimy Ridge. He returned to England, in 1917, as officer in charge of medicine at the Canadian Special Hospital, Diseases of the Chest, at Lenham, Kent. He attained the rank of major during his army service. Shortly after demobilization in 1919, he became Medical Superintendent of Queen Alexandra Sanatorium at Byron.

The steady growth of the Sanatorium at Byron, from 250 beds in 1919 to 600 beds at present, and the high standard of efficiency which it has maintained are monuments to the administrative ability of Dr. Pratten. Although burdened with the affairs of so large an institution, he was never too busy to receive his medical associates, students, patients or anyone to

whom he could give an encouraging word or helpful bit of advice.

Dr. Pratten, along with his administrative ability, was an outstanding authority on diseases of the chest. He had been a Fellow of the American College of Physicians since 1923. He was also a Fellow of the Royal College of Physicians of Canada, a member of the Western Ontario Academy of Medicine, the Academy of Medicine of Toronto, the Harvey Club of London, the Ontario Medical Association, the Canadian Medical Association, the Ontario Laennec Society, and for several years had been a member of the Executive Council of the Canadian Tuberculosis Association.

He was a retiring man and, although well known in the medical world to which he devoted his life and talents, he was unknown to many out-

side the profession. However, those who were privileged to know him sense keenly the great loss, not only to the medical world but to humanity at large, in the untimely demise of a man whose outlook on life was an inspiration to those with whom he came in contact. The funeral services were attended by many of his fellows in the Ontario Laennec Society from all parts of the Province who paid loving tribute to a beloved associate. His ashes will lie in St. Luke's-in-the-Garden, the little chapel on the Sanatorium grounds, a building dear to his heart, on the details of which he devoted much time and care; a building which he happily lived to see completed and consecrated for service.

(Furnished by JABEZ ELLIOTT, M.D., F.A.C.P., Governor for Ontario.)

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The Heart in Myxedema*†

Electrocardiograms and Roentgen-Ray Measurements before and after Therapy

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REVIEW OF THE LITERATURE

IN various articles and textbooks dealing with myxedema, very little has been said regarding the heart. The literature covering the subject of the heart in myxedema is marked by paucity, contradiction, and confusion.

In 1918 Zondek¹ introduced the term "myxedema heart" and described its characteristics as follows:

I. Before treatment with thyroid.

1. Dilatation of the left and right heart which may be of a very high degree.
2. Slow, indolent heart action with normal blood pressure.
3. Lowering of the auricular wave and the T-wave of the electrocardiogram.

II. Following treatment with thyroid.

1. Return of the heart from marked dilatation to somewhere near normal size.
2. More lively heart action and more rapid pulse without change in blood pressure.
3. Gradual return of the P- and T-waves to normal.

In this article he reported four cases which showed the above characteristics. An illustration of the roentgen-ray shadow of the heart and measurements were given in one case. The following year he presented two additional cases² giving similar results.

Assmann³ in 1919 reported a confirmatory case. Meissner⁴ in 1920 reported three cases of myxedema with cardiac studies before and after treatment. The first case showed the marked shrinkage of 4.5 cm. The second was complicated by chronic nephritis and showed no change in size. The third showed a normal heart before therapy and no change in size following it. Laubry et al⁵ reported a

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†From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital.

case of myxedema in a patient with typical angina and cardiac hypertrophy without valve lesion. There was no response to digitalis but a marked response to thyroid. No cardiac measurements were given.

In 1925 Fahr⁶ published the first paper on the heart in myxedema in this country. He stated that in spite of the neglect of the subject of heart failure in myxedema in works on both myxedema and heart disease, he believed that it was a prominent feature of all outspoken cases of myxedema. He added to the picture described by Zondek a negative *Q-R-S* complex in Lead III of the electrocardiogram which disappeared on thyroid administration, showing that it was not due to left ventricular preponderance. He described in detail one case showing a shrinkage of 6.3 cm. in the transverse diameter over a period of seven weeks of treatment. This patient had all the signs of decompensation, including orthopnea, ascites, a large liver, and râles at the lung bases. Previous trial with digitalis for three weeks had given no improvement. The signs and symptoms all cleared under thyroid medication. As a control the patient was taken off thyroid for six weeks and thereupon the size of the heart increased and again was brought back to normal by thyroid. The electrocardiogram at the beginning showed negative T_1 and T_2 and negative *Q-R-S*. These returned to normal in seven weeks.

In 1925 Christian⁷ reported 32 cases of myxedema at the Peter Bent Brigham Hospital and stated that "such a change in a heart as pictured in Fahr's case, I have never observed in any

form of cardiac disease". Twenty-two of his patients had no suggestion of a cardiac lesion by physical examination or history. Of the remaining 10, two had chronic valvular disease, five had myocarditis, two had hypertension, and three had minor cardiac disturbances. There was no case of notable cardiac enlargement. Unfortunately neither roentgen-ray nor electrocardiographic studies were given.

Willius and Haines⁸ reported a study of 162 myxedema patients. From this group 91 per cent showed no signs or symptoms of organic cardiovascular disease. The 9 per cent that did, could be accounted for on grounds other than those of myxedema. They did not mention roentgen-ray examination of the heart in any case. Fifty-five patients had electrocardiograms taken, of which 54 per cent were normal. Twenty-three per cent of the abnormalities disappeared under thyroid. In 23 per cent studies were too incomplete for conclusions. They took the position that the data presented did not justify the establishment of a cardiac syndrome characteristic of myxedema.

Case⁹ analyzed 58 patients with myxedema, without finding any to correspond to Fahr's cases.

Means, White and Krantz,¹⁰ in 1926, gaining the impression from Fahr's paper that the cardiac disturbance which he described was of frequent occurrence in myxedema, studied 48 cases of myxedema seen in the Thyroid Clinic of the Massachusetts General Hospital in the twelve previous years. The nearest approach to Fahr's case was one showing moderate enlargement and a shrinkage of 2.3 cm. over a two-week period of treatment.

The electrocardiogram showed an inverted T_2 which returned to normal under treatment. They concluded: "Myxedema heart, in the sense of Zondek and Fahr, is far from common. On the other hand we are not prepared to join those who feel that it does not exist. The evidence presented by Zondek and Fahr of a marked cardiac dilatation rapidly subsiding under thyroid seems incontrovertible, and our own case in a less striking way is one in point."

Thacher and White¹¹ that same year studied the electrocardiographic findings in 14 cases. All of these showed low T -waves, that is below 2 mm., or inverted T -waves, pulse rate average of 68, P -waves present in every case, but often small, and Q - R - S complexes of low potential which in some cases increased, as did the T -waves, with thyroid. There was no abnormal axis deviation and no auriculoventricular or intraventricular block. The P - R interval was less than 0.18 second except in one case where it was 0.20 second. There was considerable parallelism between the height of the T -waves and the level of basal metabolic rate. Thacher and White concluded that myxedema results in an abnormal and more or less characteristic electrocardiogram corrected by thyroid therapy.

From this same clinic, Sprague and White¹² reported that hypothyroidism was a common cause of low voltage in the electrocardiogram. Of the 57 cases studied, myocardial failure from arteriosclerosis accounted for 34 and hypothyroidism for 10. The low voltage of the latter disappeared in those cases reacting favorably to thyroid medication.

Also in 1926 Zins and Rösler¹³ reported a case of myxedema heart and cardiac insufficiency in a woman of 47, being reduced 3.3 cm. after three weeks of thyroid. Schittenhelm and Eisler¹⁴ presented a case with reduction of 3.3 cm. in the heart size along with return of small P -waves and negative T -waves to normal.

Fahr¹⁵ returned to the subject in 1927 with a review of his first case and five additional cases of large hearts shrinking with the taking of thyroid. The cases were well substantiated with roentgen-ray findings (table 1). He says, "Willius and Haines' conclusions are very hard to understand. With the largest material of myxedema cases in the world they have been unable to find a single case of cardiac failure attributable to myxedema, whereas in other clinics where the amount of material is very much smaller, numerous cases of heart failure, unquestionably due to the same factor as the myxedema, have been found. In the past four years we have seen just six cases of myxedema at the General Hospital and the University Hospital. All six cases showed more or less heart failure, the symptoms and signs of which receded partially or completely on thyroid medication." In three of his six cases such signs of cardiac failure as râles at the bases, big liver, and ascites were observed. In the other three, edema, dyspnea, etc., could be part of the myxedema picture without postulating cardiac failure.

From the Washington University Clinics¹⁶ in 1929 came the report of a case of myxedema with cardiac decompensation which disappeared under thyroid medication. In a period of six

weeks the heart decreased in size 3.5 cm. The electrocardiogram showed all T -waves inverted before treatment with T_2 and T_3 becoming normal and T_1 diphasic after six weeks.

Holzman¹⁷ gave a good review of the situation and reported a case with marked cardiac enlargement (transverse diameter of heart 19.7 cm., and of chest 30.5 cm.). Electrocardiogram showed left axis deviation, low voltage and flat T_3 . In seven weeks the basal metabolic rate had risen from minus 20 to plus 9. The heart was narrower by 1.7 cm., but this change was attributed to the different positions of the diaphragm. The electrocardiogram remained unchanged. This patient had a myxedema history of twelve years' duration, and the author suggests that this may have produced a true hypertrophy rather than dilatation.

In 1930 Ziskin¹⁸ reported one case with a change in the transverse diameter of 1 cm. after four weeks of treatment. The electrocardiogram showed diphasic T_1 and T_2 and delayed P - R interval. The T -waves returned to normal with treatment. Davis¹⁹ reported a case from Fahr's clinic with a shrinkage of 6.2 cm. in six weeks. This patient also showed low T -waves and a P - R interval of 0.2 second, all of which returned to normal. Tung²⁰ reported one case showing a shrinkage of 2.2 cm. in transverse diameter of the heart. He followed the electrocardiograms of seven patients, which showed low P - and Q - R - S waves, and inverted and flattened T -waves. These returned to normal after thyroid medication. Recently Ayman, Rosenblum, and Fabron-Leser²¹ reviewed the lit-

erature and reported two of their own cases. They found decreases in the size of the heart and return to normal of small or flat P - and T -waves with treatment.

Reid and Kenway²² studied the electrocardiographic changes in 260 cases of low metabolic rate, five of which had genuine untreated myxedema. They found that there was no change characteristic of low rate, but that myxedema showed the typical changes described by others: low P - and T -waves and small Q - R - S complexes. They comment upon the fact that those who have found cardiac changes as first described by Zondek have not reported more than a small number of cases. This study made them aware of the great necessity of carefully distinguishing myxedema cases from simple low rate cases, and they suggest that insufficient distinction between these two may in itself account for the diversity of opinion regarding myxedema heart.

We have summarized in tables 1 and 2 all of the known cases of myxedema in the literature which have data regarding the heart size and electrocardiogram.

Thus we have seen that complete reports of the size of the heart in myxedema have been made in relatively few cases. Most of these were published because of a strikingly large heart or marked response to thyroid. Nowhere has any number of cases been reported as a series giving the findings of the size of the heart before and after treatment. Possibly changes in the size of the heart and in the electrocardiogram take place in many treated cases of myxedema. Conse-

TABLE I
CASES REPORTED WITH ROENTGEN-RAY MEASUREMENTS OF HEART

Author	Transverse Diameter before Treatment	Transverse Diameter after Treatment	Shrinkage	Time
	cm.	cm.	cm.	
Zondek ¹	19.7	14.0	5.7	8 weeks
Assmann ³	16.7	12.7	4.0	3 "
Meissner ⁴	20.0	15.5	4.5	—
Means et al ¹⁰	14.0	11.7	2.3	16 days
Zins and Rösler ¹³	14.9	11.6	3.3	3 weeks
Schittenhelm et al ¹⁴	18.0	14.7	3.3	—
Fahr ^{6,15}	19.0	12.7	6.3	7 "
	16.0	12.3	3.3	5 "
	15.2	11.7	3.5	5 "
	14.4	13.0	1.4	5 "
	13.0	11.9	1.1	10 "
	18.2	15.9	2.3	5 "
Holzman ¹⁷	19.7	18.0	1.7	2 months
Wash. Univ. Clinics ¹⁶	22.0	18.5	3.5	6 weeks
Ziskin ¹⁸	14.0	13.0	1.0	4 "
Davis ¹⁹	19.0	12.8	6.2	6 "
Tung ²⁰	15.0	12.8	2.2	—
Ayman et al ²¹	13.1	12.0	1.1	7 "
	14.0	11.3	2.7	9 "

TABLE II
SUMMARY OF ELECTROCARDIOGRAPHIC REPORTS IN THE LITERATURE

Author	No. of Cases	Findings before Treatment	Findings after Treatment
Zondek ^{1,2}	6	Low P - and T -waves in all cases	Normal
Fahr ^{6,15}	1	Negative T_1 and T_2 ; negative Q - R - S_3	Normal
	1	Inverted T_1 , flat T_2	Normal
	1	Flat T_1	Normal
Means et al ¹⁰	1	Inverted T_2	Normal
Thacher and White ¹¹	14	All low T_2 ; several with low complexes	All normal
Wash. Univ. Clinics ¹⁶	1	Inverted T -waves	T_1 diphasic; T_2 and T_3 normal
Holzman ¹⁷	1	Left axis deviation; low voltage; flat T_3	No change
Reid and Kenway ²²	5	All low P - and T -waves; 3 with low Q - R - S	Normal
Willius and Haines ⁸	55	54% normal; 23% changes in T and Q - R - S ; 23% incomplete studies	All normal
Ziskin ¹⁸	1	Diphasic T_1 and T_2 ; delayed P - R interval	T -waves normal; P - R interval unchanged
Davis ¹⁹	1	Low T -waves; P - R = 0.2 sec.	Normal
Tung ²⁰	7	Low P and Q - R - S ; inverted and flattened T -waves	Normal
Ayman et al ²¹	2	Small or flat P - and T -waves	Normal

quently it appeared desirable to study the heart in a large series of patients with myxedema before and after treatment. Such a study would have the additional advantage of giving us statistical data for purposes of comparison with similar studies in other diseases.

METHOD AND MATERIAL

With these things in mind we began a systematic study of the heart in myxedema about three years ago. Being especially interested in the size of the heart, we tried to obtain a teleoroentgenogram before treatment and one or more after treatment with thyroid. About half of the patients included belong to a group whose treatment started before the beginning of this study but who had had measurements of the heart and electrocardiograms taken before treatment. These patients were recalled and the cardiac studies repeated.

All but one of the cases reported are patients who were studied in the hospital and had repeated metabolism tests done. They were carefully separated from cases of simple low metabolic rate showing no clinical evidence of myxedema. Cases of postoperative myxedema or cases where there was any question regarding the diagnosis were excluded. Any case of luetic or rheumatic heart disease was excluded, but cases with possible hypertensive heart disease were included.

ROENTGEN-RAY STUDIES

The available teleoroentgenograms were remeasured and those taken before and after thyroid compared with special reference to the position of the diaphragm, rotation of film, and sim-

ilarity of points of measurement. Special attention was also paid to the internal diameter of the chest. Assuming that a larger diameter on the repeat plate indicates a greater degree of inspiration, then the diaphragm may be assumed to be at least as low or lower than in the first plate. Since a low diaphragm gives an apparent decrease in heart size and a high diaphragm an apparent increase, it was necessary to repeat the roentgen-ray examination of the heart in several instances on account of the position of the diaphragm. It may be noted that in table 3, the chest diameter of seven cases is found to be more than 0.5 cm. greater in the teleoroentgenograms after thyroid medication than in the one before medication. However, only two of these cases (E. J. and J. W.) belonged to the group with a significant change in the size of the heart. Direct comparison of the plates for any given case showed very little variation in the position of the diaphragm. In only one instance (R. M.) was the diaphragm of the repeat plate lower by a whole space than in the first plate. It is therefore correct to state that errors due to position of the diaphragm did not play an important rôle in these cases.

In table 3 are given the complete cardiac measurements in 30 patients with myxedema, before and after treatment with thyroid extract. A total of 86 teleoroentgenograms is recorded. Table 4 summarizes the changes in the size of the heart and in the blood pressure as a result of treatment. Both tables are arranged in the order of the degree of shrinkage in the transverse diameter of the heart.

TABLE III
MEASUREMENTS OF THE HEART IN 30 PATIENTS WITH MYXEDEMA
BEFORE AND AFTER THYROID MEDICATION

Initials	Right	Left	Trans. Diam.	Length	Base	Half Diam. Chest	Time Interval*
Mrs. N. C.	6.5	12.8	19.3	18.0	11.9	13.0	
	6.2	11.9	18.1	16.8	10.7	12.7	12 days
	3.2	9.2	12.4	13.6	7.6	12.8	6 months
Mr. R. M.	6.8	14.0	21.4	19.8	12.6	15.8	
	4.2	11.5	15.7	11.5	11.7	16.0	6 weeks
Mrs. B. S.	4.7	11.8	16.5	16.8	12.1	13.2	
	3.5	10.1	13.6	15.1	9.2	13.3	3 weeks
	4.9	6.5	11.1	14.0	9.2	12.6	2½ months
	3.3	8.1	11.4	13.1	10.8	12.8	8½ months
Mr. E. J.	5.3	14.1	19.4	17.9	11.5	14.7	
	5.0	12.8	17.8	17.4	10.7	14.8	10 days
	3.7	13.2	16.9	17.1	9.6	14.6	3 weeks
	3.5	12.0	15.5	17.5	11.7	15.3	5 months
Mrs. J. P.	5.9	8.7	14.6	13.8	9.9	11.5	
	4.1	7.1	11.2	12.5	10.1	11.4	2 weeks
	3.5	7.8	11.3	13.0	9.5	11.1	5 weeks
Mrs. L. C.	4.2	9.9	14.1	15.0	9.8	12.8	
	3.7	9.5	13.2	13.9	10.2	11.5	6 weeks
	3.2	7.7	10.9	12.6	8.3	12.5	5 years
Mrs. A. P.	7.0	9.3	16.3	16.0	8.1	12.2	
	5.5	9.5	15.0	16.2	7.5	12.1	10 days
	5.3	8.3	13.6	13.5	10.3	12.5	3 months
	4.3	9.5	13.8	13.1	9.0	12.4	5 months
Mrs. E. G.	4.4	11.2	15.6	15.3	10.6	13.2	
	4.4	8.7	13.1	14.5	8.2	13.2	4 years
Mrs. R. W.	5.2	10.7	15.9	15.2	10.3	12.3	
	5.5	9.8	15.3	14.8	9.5	12.2	2 weeks
	4.3	9.3	13.6	14.8	9.5	12.1	5 months
Mrs. J. R.	5.9	9.4	15.3	14.2	10.5	12.9	
	4.5	9.5	14.0	12.5	8.6	13.1	3½ weeks
	4.8	8.3	13.1	12.8	5.7	13.0	4 months
	5.0	8.5	13.5	13.2	10.7	13.0	11 months
Mrs. E. Mc.	5.5	9.1	14.6	14.2	9.1	12.0	
	5.8	8.4	14.2	13.9	7.0	12.1	1 week
	4.6	7.9	12.5	11.8	7.0	12.2	3 weeks
	4.2	8.9	13.1	12.5	9.5	12.4	7 months
	4.5	8.5	13.0	12.0	9.6	12.4	9 months
	4.2	9.2	13.4	13.4	13.7	12.8	1½ years
Mrs. A. F.	4.7	7.6	12.3	13.1	10.5	12.0	
	3.8	6.8	10.6	11.8	9.3	10.4	1 year
	2.8	7.4	10.2	12.5	10.0	10.9	1½ years
Mrs. A. H.	6.3	8.2	14.5	14.5	10.7	11.3	
	5.0	7.5	12.5	13.0	9.7	10.8	1 year

*After the beginning of medication.

TABLE III—(Continued)

Initials	Right	Left	Trans. Diam.	Length	Base	Half Diam. Chest	Time Interval*
Mrs. A. Mc.	4.1	8.7	12.8	13.0	8.6	12.9	
	3.1	8.8	11.9	13.0	8.7	12.9	3 weeks
	3.2	8.3	11.5	14.0	10.2	12.7	4 months
	3.3	7.5	10.8	12.8	6.1	12.3	5 months
	3.5	7.6	11.1	12.0	8.2	12.6	1 year
Mrs. L. Mc.	4.7	8.3	13.0	13.6	8.8	11.0	
	4.0	7.1	11.1	12.0	9.0	10.8	1 year
Mrs. A. G.	4.3	8.3	12.6	13.1	8.6	11.2	
	3.0	7.9	10.9	12.1	8.0	11.5	1 month
	3.2	8.2	11.4	12.1	7.2	11.8	11 months
Miss C. Mc.	5.0	10.7	15.7	15.0	11.5	14.3	
	5.7	8.7	14.4	14.7	6.8	14.2	9 days
	4.2	9.8	14.0	15.0	7.6	14.1	3 weeks
Mrs. E. M.	4.0	9.5	13.5	14.0	8.5	12.5	
	3.8	8.3	12.1	13.5	7.2	11.5	15 months
	3.4	9.4	12.8	13.3	7.2	12.3	7 years
Mrs. D. M.	4.7	6.8	11.5	12.4	8.6	11.8	
	3.8	6.3	10.1	11.3	6.7	11.6	10 months
Mr. J. W.	4.8	8.6	13.4	13.5	10.8	14.4	
	3.5	8.7	12.2	12.1	5.9	14.8	5 years
Mrs. E. S.	4.0	10.5	14.5	14.5	9.0	13.3	
	3.5	10.2	13.7	13.7	5.5	14.3	2½ years
Mrs. M. F.	4.1	8.8	12.9	13.5	8.9	12.7	
	5.1	7.6	12.5	14.6	10.5	12.7	2 months
	4.4	7.7	12.1	13.2	9.7	12.4	10 months
Mrs. M. B.	3.7	8.7	12.4	14.0	10.0	12.5	
	3.7	8.0	11.7	12.7	6.9	12.6	4 years
Mrs. E. O.	3.7	9.2	12.9	13.7	9.3	11.9	
	4.1	8.4	12.5	11.0	8.5	12.6	3 weeks
	4.3	8.2	12.5	12.7	6.3	12.6	14 months
Miss A. P.	5.0	9.0	14.0	12.5	9.0	12.5	
	5.6	8.0	13.6	13.6	6.5	12.5	3 years
Mrs. M. Mc.	4.9	10.1	15.0	14.8	10.0	13.1	
	3.8	10.9	14.7	14.6	6.8	12.9	1½ years
Mrs. M. L.	5.3	9.3	14.6	15.2	8.5	12.7	
	3.8	10.5	14.3	15.0	8.7	12.5	3 years
Mrs. J. C.	3.2	10.1	13.3	14.3	9.3	12.8	
	2.8	10.6	13.4	13.8	5.2	13.3	3 years
Mrs. E. D.	4.1	9.9	14.0	14.2	9.9	14.0	
	5.1	9.0	14.1	14.8	5.3	14.7	5 years
Mr. J. G.	3.1	10.4	13.7	12.7	8.5	12.8	
	2.7	11.5	14.2	14.8	6.6	12.9	3 months
	3.6	11.1	14.1	15.3	7.1	13.2	4 years

*After the beginning of medication.

TABLE IV
CHANGE IN SIZE OF HEART AND IN BLOOD PRESSURE AFTER THYROID MEDICATION
IN 30 PATIENTS WITH MYXEDEMA

Patient	Age	Basal Metab. Rate	Half Trans. Chest Diam.	Trans. Heart Diam. before Rx	Max. Heart Change after Rx	Time Interval for Change	Blood Pressure before Rx	Blood Pressure after Rx
Mrs. N. C.	46	-28	13.0	19.3	6.9	6 mo.	180/130	148/104
Mr. R. M.	45	-37	15.8	21.4	5.7	6 wk.	175/115	-
Mrs. B. S.	42	-34	13.2	16.5	5.4	2½ mo.	118/ 90	110/ 70
Mr. E. J.	77	-30	14.7	19.4	3.9	5 mo.	145/ 90	125/ 70
Mrs. J. P.	49	-36	11.5	14.6	3.4	2 wk.	180/120	125/ 75
Mrs. L. C.	53	-45	12.8	14.1	3.2	5 yr.	140/ 70	150/ 70
Mrs. A. P.	44	-40	12.2	16.3	2.7	3 mo.	138/116	160/104
Mrs. E. G.	48	-35	13.2	15.6	2.5	4 yr.	120/ 65	155/ 90
Mrs. R. W.	36	-38	12.3	15.9	2.3	5 mo.	160/110	146/ 84
Mrs. J. R.	43	-28	12.9	15.3	2.2	4 mo.	165/110	120/ 76
Mrs. E. Mc.	70	-29	12.0	14.6	2.1	3 wk.	180/100	180/ 90
Mrs. A. F.	42	-39	12.0	12.3	2.1	1½ yr.	115/ 80	-
Mrs. A. H.	51	-30	11.3	14.5	2.0	1 yr.	148/100	154/ 94
Mrs. A. Mc.	47	-17	12.9	12.8	2.0	5 mo.	140/100	126/ 80
Mrs. L. Mc.	33	-30	11.0	13.0	1.9	1 yr.	125/ 80	115/ 75
Mrs. A. G.	45	-43	11.7	12.6	1.7	1 mo.	125/ 80	126/ 80
Miss C. Mc.	50	-29	14.3	15.7	1.7	3 wk.	130/ 90	-
Mrs. E. M.	41	-24	12.5	13.5	1.4	15 mo.	130/ 70	110/ 65
Mrs. M. D.	49	-31	11.8	11.5	1.4	10 mo.	142/ 76	120/ 78
Mr. J. W.	63	-32	14.4	13.4	1.2	5 yr.	160/ 75	120/ 70
Mrs. E. S.	43	-35	13.3	14.5	0.8	2½ yr.	110/ 85	138/ 80
Mrs. M. F.	42	-19	12.8	12.9	0.8	10 mo.	128/ 86	134/ 82
Mrs. M. B.	32	-45	12.5	12.4	0.7	4 yr.	112/ 65	110/ 70
Mrs. E. O.	70	-20	11.9	12.9	0.4	14 mo.	190/130	154/110
Miss A. P.	56	-34	12.5	14.0	0.4	3 yr.	160/120	178/106
Mrs. M. Mc.	55	-31	13.1	15.0	0.3	1½ yr.	165/115	148/ 90
Mrs. M. L.	49	-16	12.3	14.6	0.3	3 yr.	140/100	154/102
Mrs. J. C.	56	-31	12.8	13.3	-0.1	3 yr.	150/ 90	210/110
Mrs. E. D.	42	-35	14.0	14.0	-0.1	5 yr.	120/ 80	100/ 68
Mr. J. G.	53	-25	12.8	13.7	-0.4	4 yr.	130/ 90	128/ 76

Considering any heart above normal size where the transverse cardiac diameter is greater than half the internal diameter of the chest, then we find that 25 of the 30 patients had enlarged hearts, as follows:

Transverse cardiac diameter minus one-half internal chest diameter cm.	No. of cases
0 - 1.0	5
1.0 - 1.9	7
2.0 - 2.9	4
3.0 - 3.9	5
4.0 - 4.9	2
5.0 - 5.9	1
6.0 +	1

In the remaining five cases the trans-

verse cardiac diameter was either equal to or less than half the internal chest diameter.

Of the 30 cases, 20 showed a maximum decrease in transverse diameter of the heart after treatment of more than one centimeter and seven of less than a centimeter, distributed as follows:

Decrease in transverse cardiac diameter cm.	No. of cases
0.1 - 0.9	7
1.0 - 1.9	6
2.0 - 2.9	8
3.0 - 3.9	3
4.0 - 4.9	0
5.0 - 5.9	2
6.0 - 6.9	1

The remaining three cases showed increases of 0.1 to 0.4 cm. The age of the patient bore no relation to the change in the heart size under therapy. As for sex, there were only four males in the series. The presence of hypertension did not prevent the heart from shrinking. In fact, nine of the 20 patients who showed changes in the transverse cardiac diameter of more than a centimeter had some degree of hypertension before treatment. However, in these cases the repeat teleoroentgenograms were obtained usually less than six months after the beginning of treatment so that the factor of hypertrophy due to long-standing hypertension did not obscure the picture. Moreover, the hypertension disappeared in five cases. There is a close relationship between the degree of cardiac enlargement before treatment and the amount of shrinkage in the heart under treatment. The greatest changes in the size of the heart occurred in the large hearts. Expressed mathematically, the coefficient of correlation between the degree of cardiac enlargement and the degree of cardiac shrinkage is -0.70 ± 0.067 for all the cases, and -0.83 ± 0.050 for the 20 cases which decreased more than one centimeter. Both figures are highly significant statistically. The tendency in general was for the heart to approach normal size under therapy. In the few cases that this was not fulfilled, usually some degree of hypertension persisted.

The decrease in size of the heart in myxedema under thyroid medication is a slow and progressive procedure, as indicated in table 3. Twelve patients had serial teleoroentgenograms

during the first year of treatment. Ten of these showed progressive shrinkage in size of the heart, reaching a maximum in three weeks to ten months after the beginning of treatment. Two cases reached their maximum in three weeks, six in three to five months, one in six months and one in ten months. The last had no examination in the interval between two months and ten months after treatment, so that the maximum change might well have occurred before ten months.

As indicated in table 3 the changes in the heart occurred in all diameters. However, measurements of the length and base of the heart are difficult to make and are subject to greater errors than the transverse cardiac diameter. Consequently the latter is used in judging the degree of cardiac shrinkage. As a matter of fact, the actual shrinkage in volume of the heart was greater in some instances than the decrease in transverse diameter indicated. Assuming that the surface area of the heart in the teleoroentgenogram is a more accurate measure of the volume of the heart than the transverse cardiac diameter, we measured the surface area of the heart of the first two cases (N. C. and R. M.) before and after treatment. In the first case (figure 1) the maximum change in surface area was from 161.6 sq. cm. to 77.6 sq. cm., a decrease of 52 per cent. The decrease in transverse cardiac diameter was 36 per cent. In the second case (figure 2) the maximum change in surface area was from 190.8 sq. cm. to 137.4 sq. cm., a decrease of 28 per cent. The transverse diameter decreased 26.6 per cent.

As mentioned above, the transverse

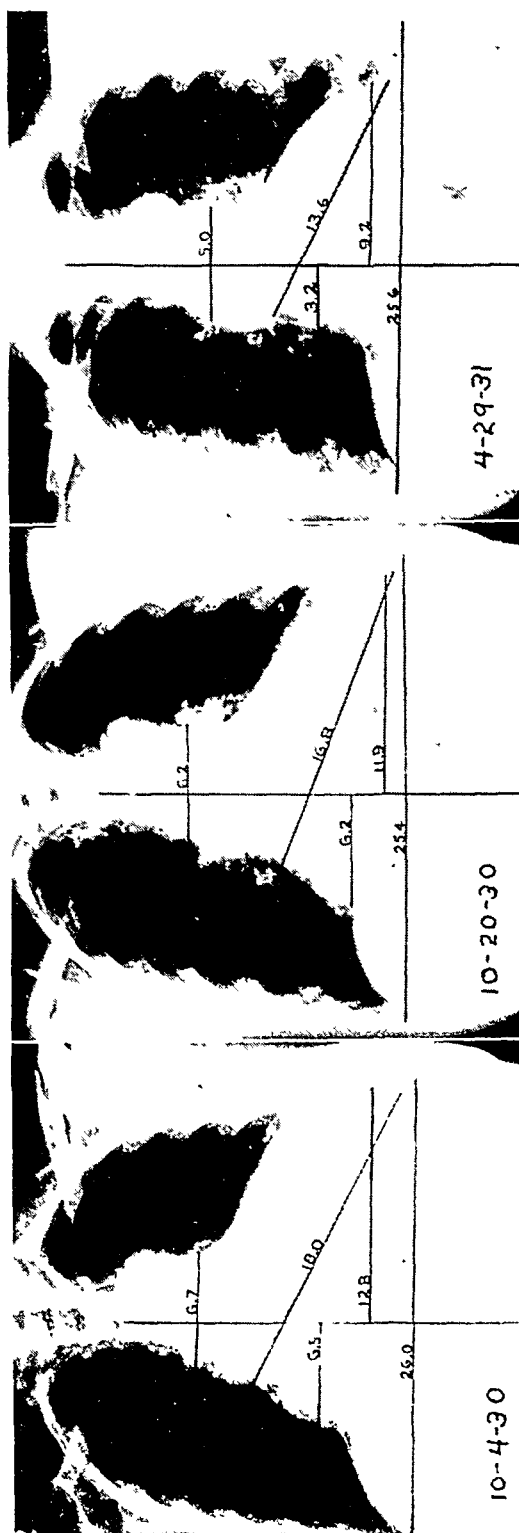


FIG. 1. Changes in the teleoroentgenogram of patient (N. C.), at intervals of two weeks and six months after thyroid medication. The level of basal metabolism was minus 28 per cent; two weeks later it was minus 4 per cent; and six months later it was minus 3 per cent.

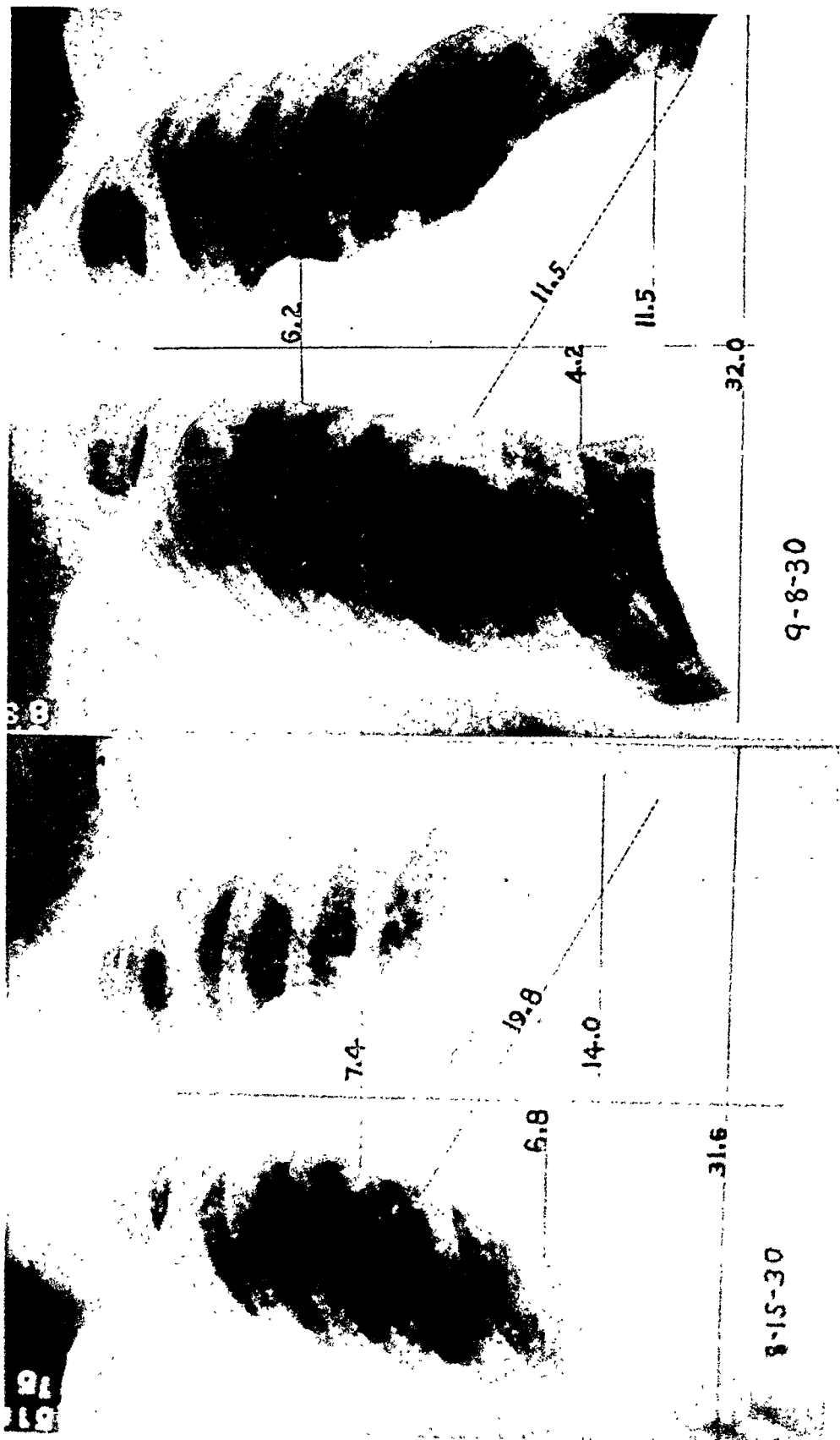


FIG. 2. Changes in the teleoroentgenogram of patient (R. M.), six weeks after thyroid medication. The level of basal metabolism was minus 37 per cent; and six weeks later it was plus 5 per cent.

diameter in ten cases decreased less than one centimeter or actually increased slightly under medication. The failure of these cases to show changes in the size of the heart may be explained for the most part by two factors. In the first place five of the patients (E. O., A. P., M. Mc., M. L., and J. C.) had persistent hypertension. Four of these had the first reëxamination of the heart one and one-half to three years after the beginning of treatment, and the fifth had the first reëxamination at three weeks and the second reëxamination at fourteen months. In these five cases, true hypertrophy might have been present at the beginning; or, if shrinkage of the heart had actually taken place, the cardiac hypertrophy due to hypertension during the long intervals between examinations might have masked it. The latter course of events was observed in one case (E. Mc.). This patient had a hypertension of 180 mm. of Hg systolic and 90-100 mm. diastolic. The transverse cardiac diameter was reduced from 14.6 cm. to 12.5 cm. in three weeks of treatment. At the end of nine months the transverse diameter was 13.0 cm. and at a year and one-half it was 13.4 cm.

The second explanation for the failure of this group of cases to show cardiac shrinkage is based on the above finding that the amount of shrinkage of the heart is proportional to the degree of cardiac enlargement. Consequently patients with normal hearts are not to be expected to show much change. Three (M. F., M. B., and E. D.) of the five remaining cases of this group had normal-sized hearts at the beginning of treatment. The fourth

case (E. S.) had a normal-sized heart after the slight reduction in size had taken place.

It may be said in passing that the more carefully one follows patients with myxedema the more often will one find cardiac changes under treatment. Thus, of the 15 patients followed from the beginning of treatment, with this matter in mind, nine showed a decrease in transverse cardiac diameter of more than 2 cm., four of 1 to 2 cm., one of 0.8 cm., and the other of 0.4 cm.

BLOOD PRESSURE

Under thyroid medication the blood pressure underwent changes in 23 cases, either systolic, diastolic, or both, no change in four cases and was not followed in three. The systolic pressure dropped 10 mm. or more in 13 cases, rose 10 mm. or more in seven cases and underwent an insignificant change in seven. The diastolic pressure dropped 10 mm. or more in 14 cases, rose 10 mm. or more in two, and underwent an insignificant change in 11. The net result was a slight increase in pulse pressure. The latter rose 10 mm. or more in 13 cases, dropped 10 mm. or more in six, and underwent an insignificant change in eight. The patients with hypertension showed more marked changes than the remainder. Of the 14 patients with hypertension that were followed, five developed a normal blood pressure after treatment and six reached a lower level of hypertension, particularly in diastolic pressure. Only one patient with normal blood pressure before treatment developed hypertension after treatment.

ELECTROCARDIOGRAMS

The matter of the electrocardiographic changes in myxedema appears to be on firm ground, but it was felt worth while to report the electrocardiograms in these patients both as adding to the evidence already at hand and for purposes of correlation with the roentgen-ray findings.

Electrocardiograms were obtained in 24 patients before and after treatment and are recorded in table 5. The most common abnormality in the electrocardiogram before treatment was flattening or inversion of the *T*-waves. This occurred 14 times in all leads, eight times in two leads and twice in one lead. The *T*-waves were abnormal in one or more leads in all 24 cases. The *T*-wave in Lead II was most commonly involved, i.e., in 23 cases; *T*₁ was involved in 22 cases and *T*₃ in 15 cases. In addition, nine electrocardiograms showed axis deviation, nine

showed small complexes, one showed auricular premature beats, and one showed intraventricular block. The *P*-waves were low or flat in all but one case.

Under thyroid administration, 11 of the patients showed normal electrocardiograms at varying intervals after the beginning of treatment. Nine of these belong in the group whose hearts shrank more than one centimeter. In some instances the return to normal was delayed. In addition six lost their *T*-wave abnormalities and one lost his small complexes. Thus a total of 18 patients showed a disappearance of one or more of these abnormalities from their electrocardiograms. Four of the remaining six patients showed partial improvement of *T*-wave changes. The *P*-waves increased in size in 22 of the 24 cases. In all, 17 patients showed a complete disappearance of *T*-wave abnormalities

TABLE V
THE ELECTROCARDIOGRAM IN 24 PATIENTS WITH MYXEDEMA BEFORE AND AFTER THYROID MEDICATION*

Initials	Electrocardiogram before Treatment	Electrocardiogram after Treatment Time Interval in Parentheses
Mrs. B. S.	Low <i>T</i> all leads; low voltage.	Normal (6 wks.). Slightly slurred <i>Q-R-S</i> ₂ and <i>Q-R-S</i> ₃ (8 mos.).
Mr. E. J.	Left axis deviation; slightly inverted <i>T</i> ₁ ; flat <i>T</i> ₂ and <i>T</i> ₃ .	Partial A-V block; low <i>T</i> -waves; slight left axis deviation (2 wks.). Slightly inverted <i>T</i> ₁ ; <i>T</i> ₂ and <i>T</i> ₃ + 3 mm.; slight left axis deviation (5 mos.).
Mrs. J. P.	Slightly inverted <i>T</i> ₁ ; low <i>T</i> ₂ and <i>T</i> ₃ ; slurred <i>Q-R-S</i> .	Inverted <i>T</i> ₁ and <i>T</i> ₂ ; slight slurring <i>Q-R-S</i> (3 wks.).
Mrs. A. P.	Low voltage; low <i>T</i> -waves.	Low voltage; low <i>T</i> -waves; slight left axis deviation (2 wks.). Left axis deviation; normal <i>T</i> ₁ and <i>T</i> ₂ ; inverted <i>T</i> ₃ (4 mos.).
Mrs. E. G.	Flat <i>T</i> ₁ ; inverted <i>T</i> ₂ and <i>T</i> ₃ ; low voltage; slight left axis deviation.	S-A tachycardia; small complexes (4 yrs.).

*The *T*-waves are not recorded here. They were small in all but one case. Under medication, the *T*-waves are recorded in type.

TABLE V—(Continued)

Initials	Electrocardiogram before Treatment	Electrocardiogram after Treatment Time Interval in Parentheses
Mrs. R. W.	Diphasic T_2 ; flat T_3 ; tendency toward right axis deviation; small complexes.	Normal (9 mos.).
Mrs. J. R.	Left axis deviation; T_1 inverted; T_2 flat.	S-A tachycardia; left axis deviation; flat T_1 and T_2 (1 wk.). S-A tachycardia; left axis deviation; T_1 and $T_3 + 3$ mm.; T_2 normal (4 mos.).
Mrs. E. Mc.	Slight intra-ventricular block; inverted T_1 ; flat T_2 .	Left axis deviation (10 mos.).
Mrs. A. F.	Flat T_1 and T_2 .	Normal (3 wks.). Normal (1 yr.).
Mrs. A. Mc.	Flat T_1 ; inverted T_2 ; left axis deviation.	Normal (5 mos.).
Mrs. A. G.	Low T -waves all leads; low voltage.	Flat T -waves all leads; slight left axis deviation (1 wk.). Normal (1 yr.).
Miss C. Mc.	Inverted T_1 ; diphasic T_2 ; left axis deviation.	Low T -waves; left axis deviation (2 wks.). Low T -waves; left axis deviation (3 wks.).
Mrs. E. M.	Low T -waves all leads.	Low T -waves all leads; T_2 slightly higher (15 mos.). Normal (7 yrs.).
Mrs. M. D.	All T -waves flat.	Normal (1 yr.).
Mr. J. W.	Flat T_1 ; diphasic T_2 ; flat T_3 ; small complexes.	Normal (5 yrs.).
Mrs. L. C.	Inverted T -waves all leads; small complexes.	Normal (1 mo.).
Mrs. E. S.	Rather low voltage; low T_1 and T_2 ; flat T_3 .	Normal T_1 ; Leads II and III not obtained (2½ yrs.).
Mrs. M. F.	Flat T_1 ; inverted T_2 and T_3 .	Slight left axis deviation; low T -waves all leads (2 mos.). Low T_2 and T_3 ; slight left axis deviation (8 mos.).
Mrs. M. B.	Flat T_1 ; inverted T_2 and T_3 ; slight right axis deviation.	T -waves normal; slight right axis deviation (7 mos.).
Miss A. P.	Slight left axis deviation; inverted T_1 .	Ventricular premature beats; left axis deviation; inverted T_1 (5 mos.). Slight slurring of Q - R - S ; diphasic T_1 and T_2 ; flat T_3 (1 yr.). Marked left axis deviation; inverted T all leads (3 yrs.).
Mrs. M. L.	Slightly inverted T_1 and T_2 ; slight left axis deviation.	Low T_2 (2 wks.). Slight left axis deviation (3 yrs.).
Mrs. J. C.	Auricular premature beats; inverted T_1 and T_2 .	Normal (3 yrs.).
Mrs. E. D.	Flat T -waves all leads; low voltage.	Inverted T_1 ; T_2 and $T_3 + 6$ mm.; slight left axis deviation; inverted Q - R - S ; (5 yrs.).
Mr. J. G.	Flat T_2 .	Moderate left axis deviation (5 yrs.).

whereas seven retained some abnormality. Small complexes were retained in only one of the nine cases. Six patients retained axis deviation and five additional patients developed this abnormality with treatment. However, six of these 11 patients had hypertension at the beginning of treatment, and six were in the group whose hearts decreased less than one centimeter. On the other hand the three patients who lost their axis deviation belonged in the group whose hearts decreased more than one centimeter. In general it would seem that the cases which showed the most marked shrinkage in the shadow of the heart were the ones whose electrocardiograms showed the most return to normal.

It has been suggested by Nobel, Rosenblüth and Samet²³ that resistance of the myxedema skin is the factor causing the abnormal electrocardiographic findings. By using needle electrodes to overcome skin resistance, they were able to change abnormal electrocardiograms to normal. The fallacy of this contention is that if the changes in the electrocardiogram are due to resistance of the skin, then all the complexes should be equally affected. On the contrary, in myxedema the T-waves show the most marked deviation from the normal. Dr. Paul D. White was good enough to test out the suggestion of Nobel et al by obtaining electrocardiograms with the usual electrodes and then with needle electrodes in two patients. The results are illustrated in figure 3. In one case the resistance was actually higher with needle electrodes than with the usual electrode, in the other the resistance

was about the same. With greater resistance a looser string was required so that overshooting and exaggerated complexes occurred but the character of these complexes was unchanged. Consequently electrocardiographic abnormalities are probably due to changes in the heart itself and not in the skin.

OTHER FINDINGS

Fourteen patients at time of entry into the hospital showed no abnormality on auscultation. Four showed systolic murmurs, two had extra systoles and the remainder presented sounds of faint or poor quality. Cardiac enlargement as gauged by physical examination was found in nine cases. The size of the heart was under-measured on physical examination in 15 cases and in eight of these the undermeasurement was great enough to cause the diagnosis of normal-sized heart, whereas the roentgen-ray showed an enlarged heart.

Several of the cases in the literature presented signs of definite cardiac decompensation. Fahr^{6,15} emphasizes cardiac failure as part of the picture of "myxedema heart". To be sure, many of our patients showed various degrees of peripheral edema but this may be accounted for on the basis of myxedema alone. Four patients showed evidence suggestive of cardiac failure, as follows: one (R. M.) showed crepitant râles at the lung bases and pitting edema over the extremities and sacrum; one (E. J.) showed a small amount of fluid in the right pleural cavity, palpable liver edge, and pitting edema of the extremities; and two (J. C. and E. O.) showed crepitant râles at the lung bases, palpable liver

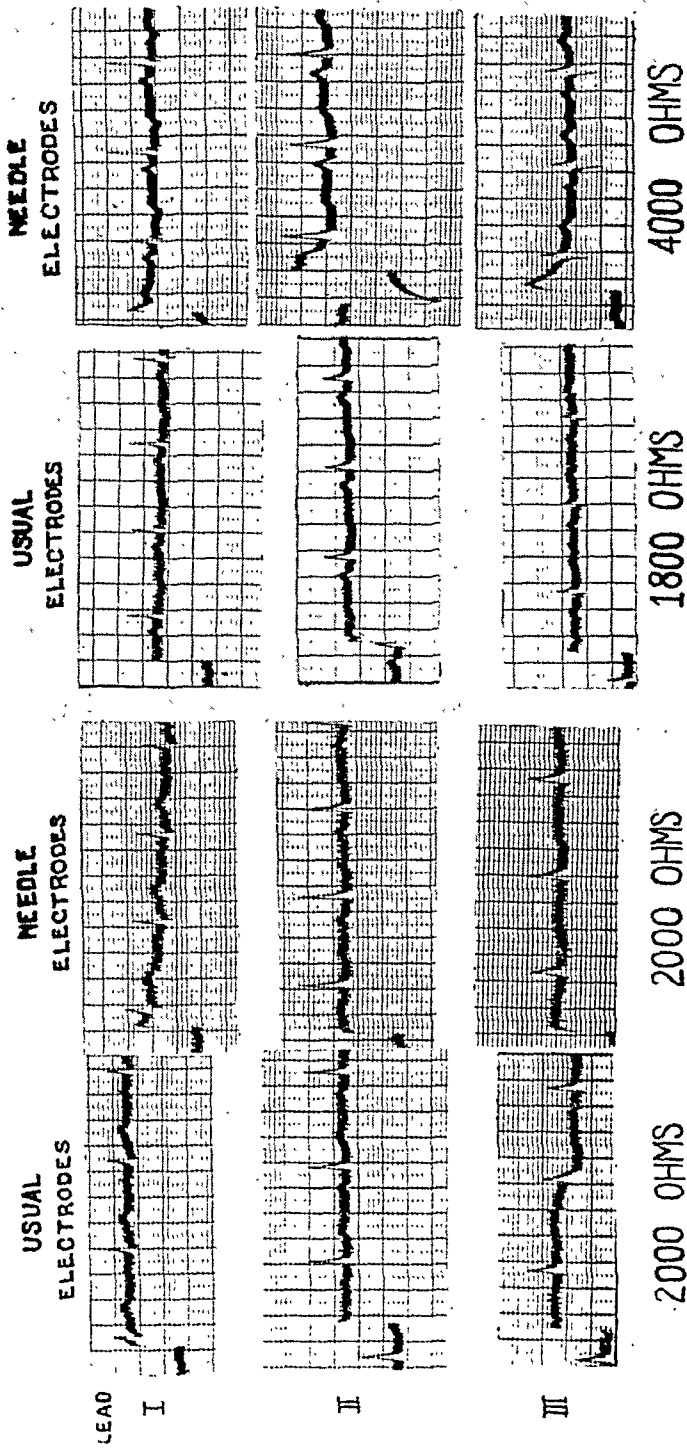


FIG. 3. Illustration of the effect of needle electrodes on the electrocardiogram. In one case the skin resistance was the same with needle electrodes as with the usual electrodes; and in the other the skin resistance was greater with needle electrodes than with the usual electrodes.

edge, and pitting edema. The evidence for cardiac failure was not conclusive in any of these. All the signs disappeared on rest and thyroid medication. The blood pressure was moderately elevated in each of these cases, and the peripheral vessels sclerosed in three. The patient presenting the most evidence of congestive failure (R. M.) died suddenly seven months after leaving the hospital, cause undetermined.

DISCUSSION

One gathers the impression from a study of the literature that the cases reported by Zondek, Fahr, and others, in which roentgen-ray findings or photographs of the roentgenograms are given, are all thoroughly genuine. We believe that Fahr emphasizes the point of cardiac failure to a greater extent than his published findings warrant. In three of his cases,¹⁵ dyspnea and edema could well be part of the general picture of myxedema rather than due to cardiac failure. Our impression of the report by Willis and Haines⁶ is that their cases were not thoroughly worked up. The inclusion of patients with low metabolism but without myxedema may account for the finding of normal electrocardiograms in 54 per cent of their cases.

Moreover it is worth noting that Willis and Haines,⁶ and Christian,⁷ the two who are most emphatic in denying the existence of "myxedema heart" fail to mention roentgen-ray studies of the heart size. As indicated above, the heart in myxedema is frequently under-measured by physical examination before therapy is started. Consequently change in the size of

the heart might easily be missed, unless serial teleoroentgenograms are obtained.

Our studies lead us to believe that the heart in myxedema is usually enlarged and decreases in size when thyroid is administered and that the change in the size of the heart is of diagnostic importance. Cardiac failure due to myxedema is uncommon, and slight if present. It is practically always associated with hypertension and arteriosclerosis.

The nature of the decrease in heart size is difficult to understand, mainly because so little is known of the pathology of the heart in myxedema.* The best and most complete pathological description of myxedema cases is to be found in the report of the Clinical Society of London published in 1888.²⁵ The findings in 20 cases are reviewed. The left ventricle of the heart was hypertrophied in a third of the cases. In more than half there was atheroma of the arteries. Microscopic descriptions are given in only nine cases. Three of these showed evidence of interstitial myocarditis.

At the Massachusetts General Hospital we have been able to trace the records of five autopsies on myxedema patients. Three died as a result of complicating infections, one died of an unknown cause, and one died of hypertensive and arteriosclerotic heart disease before the myxedema could be treated. Four showed interstitial edema with more or less fibrosis of the heart muscle, and the fifth showed fibrosis only. Two of the patients had not

*The nature of the heart in myxedema is discussed by one of us (J. H. M.) in a recent article.

received any thyroid medication. It seems likely that the edematous condition present in other tissues in myxedema is also present in the heart muscle. Therefore the changes in the heart should be regarded as part of the picture of myxedema and not as a separate entity.

Experimentally, the removal of thyroids in animals causes gross alterations in the cardiovascular system. Among others, Goldberg²⁶ showed that sheep and goats made cretinoid by removal of their thyroids, developed cardiac dilatation and a flabby myocardium.

On the basis of the above facts, one is justified in making the tentative assumption that administration of thyroid extract decreases the size of the heart in myxedema by causing the loss of interstitial edema and by increasing the muscle tonus.

It has been suggested that pericardial effusion may account for the size of the heart and that disappearance of fluid with thyroid medication may account for the apparent cardiac shrinkage. This is of interest in view of the finding of the London Committee²⁵: "Anasarca to a slight degree was not uncommon, though in no instance was it excessive. On the other hand, passive effusions into serous cavities, sometimes to a considerable amount, were frequently noted." While they do not specifically report any case with pericardial effusion, their findings suggest that this condition may occur. Both of our autopsied patients who did not receive thyroid before death had fluid in the pericardial sac—one a small amount (150 c.c.) and the other a large amount (1+ liters). The latter pa-

tient possessed the complicating factors of hypertension and arteriosclerosis. Moreover, Goldberg²⁶ found pericardial fluid in seven of 18 sheep with experimental myxedema. In most cases, however, neither the clinical findings nor the roentgen-ray picture of the heart are consistent with significant amounts of pericardial fluid.

CONCLUSIONS

The heart is generally enlarged in myxedema. After thyroid medication, the size of the heart, in most cases, undergoes a progressive shrinkage, which reaches its maximum as a rule in three to six months. This decrease is of diagnostic value. The amount of reduction in the size of the heart is proportional to the degree of cardiac enlargement. The failure of some patients to show cardiac change after thyroid medication may be explained on the basis either of long standing hypertension or of the fact that the heart is not enlarged before treatment.

The blood pressure in myxedema is often elevated above normal. With treatment there is a tendency for both systolic and diastolic pressures to fall, particularly the latter. The net result is a slight increase in pulse pressure. The most marked reductions in blood pressure occur in patients with hypertension.

The electrocardiogram in myxedema is always abnormal. The most common abnormality is a flattening or inversion of the *T*-waves, particularly in Lead II. In addition, abnormal axis deviation and small *P* and *Q-R-S* complexes are common. On thyroid treatment, many of the abnormalities disappear wholly or in part. The greatest

return to normal occurs in those patients with the most marked shrinkage in the size of the heart. The abnormalities in the electrocardiograms are probably not due to increased skin resistance but to changes in the conduction system of the myocardium.

"Myxedema heart" in the sense of cardiac enlargement which undergoes shrinkage on thyroid medication is common; in the sense of Zondek and Fahr, i.e., cardiac enlargement in association with congestive failure, it is rare. The heart changes are to be

regarded as part of the picture of myxedema, not as a separate cardiac entity. The patients with findings suggestive of cardiac failure usually have hypertension and arteriosclerosis.

The change in the heart with thyroid treatment is probably due to increased muscle tonus and loss of interstitial edema. In an occasional case the loss of pericardial fluid may account for this change.

We are indebted to Dr. P. D. White for his valuable assistance during the course of this work.

BIBLIOGRAPHY

- ¹ZONDEK, H.: Das Myxödemherz, München med. Wchnschr., 1918, lxxv, 1180-1182.
- ²ZONDEK, H.: Das Myxödemherz, (II. Mitteilung), München med. Wchnschr., 1919, lxxvi, 681-683.
- ³ASSMANN, H.: Das Myxödemherz, München med. Wchnschr., 1919, lxxvi, 9.
- ⁴MEISSNER, R.: Zur Klinik des Myxödemherzens, München med. Wchnschr., 1920, lxxvii, 1316.
- ⁵LAUBRY, C., MUSSIO-FOURNIER, J. C., and WALSER, J.: Syndrome angineux et insuffisance thyroïdienne, Bull. et mém. Soc. méd. de hôp. de Paris, 1924, xlviii, 1592-1598.
- ⁶FAHR, G.: Myxedema heart, Jr. Am. Med. Assoc., 1925, lxxxiv, 345-349.
- ⁷CHU-CHAN, H. A.: The heart and its management in myxedema, Rhode Island Med. Jr., 1925, viii, 109-113.
- ⁸WILLIUS, F. A., and HAINES, S. F.: The status of the heart in myxedema, Am. Heart Jr., 1925, i, 67-72.
- ⁹CASE, C. E.: An analysis of fifty-eight cases of myxedema, Clifton Med. Bull., 1925, vi, 112.
- ¹⁰MEANS, J. H., WHITE, P. D., and KRANTZ, C. E.: Observations on the heart in myxedema, with special reference to dilatation and angina pectoris, Boston Med. and Surg. Jr., 1926, cxxxv, 455-460.
- ¹¹THACHER, C., and WHITE, P. D.: The electrocardiogram in myxedema, Am. Jr. Med. Sci., 1926, clxxi, 61-66.
- ¹²SPRAGUE, H. B., and WHITE, P. D.: The significance of electrocardiograms of low voltage, Jr. Clin. Invest., 1926, iii, 109-121.
- ¹³ZINS, B., and RÖSLER, H.: Kasuistischer Beitrag zur Beeinflussung des Myxödemherzens durch Thyreoidin, Wien. klin. Wchnschr., 1926, xxxix, 1360-1361.
- ¹⁴SCHITTENHELM, A., and EISLER, B.: Über die Wirksamkeit des Thyroxins (Scher-ing) bei Endokrin bedingten Störungen, Klin. Wchnschr., 1927, vi, 1935-1938.
- ¹⁵FAHR, G.: Myxedema heart, Am. Heart Jr., 1927, iii, 14-30.
- ¹⁶DUDEN, C. W.: Myxedema with cardiac decompensation and hypertension which disappeared under thyroid medication, Jr. Missouri Med. Assoc., 1929, xxvi, 25-27.
- ¹⁷HOLZMAN, J. E.: Myxedema heart, with report of two cases, Am. Heart Jr., 1929, iv, 351-366.
- ¹⁸ZISELIN, T.: Angina pectoris associated with myxedema heart, U. S. Vet. Bur. Med. Bull., 1930, vi, 24-26.
- ¹⁹DAVIS, J. C.: Myxedema heart, with report of one case, Ann. Int. Med., 1931, iv, 733-741.

- ²⁰TUNG, C. L.: The status of the heart in myxedema, *Am. Heart Jr.*, 1931, vi, 734-742.
- ²¹AYMAN, D., ROSENBLUM, H., and FALCON-LESSES, M.: "Myxedema Heart" without evidence of cardiac insufficiency; report of two cases, *Jr. Am. Med. Assoc.*, 1932, xcvi, 1721-1725.
- ²²REID, W. D., and KENWAY, F. L.: Electrocardiographic signs associated with low basal metabolism, *Endocrinology*, 1929, xiii, 191-204.
- ²³NOBEL, E., ROSENBLÜTH, A., and SAMET, B.: Das Elektrokardiogramm des kindlichen Myxödems, *Ztschr. f. d. ges. exper. Med.*, 1924, xliii, 332-341.
- ²⁴MEANS, J. H.: Hypothyroid heart disease, *N. E. Jr. Med.*, 1933, ccviii, 541-542.
- ²⁵Trans. Clin. Soc. London, Report of a Committee of the Clinical Society of London, nominated Dec. 19, 1883, to investigate the subject of myxedema; Supplement to Vol. 21, London, 1888.
- ²⁶GOLDBERG, S. A.: Changes in organs of thyroidectomized sheep and goats, *Quart. Jr. Exper. Physiol.*, 1927, xvii, 15-30.

Heredit^y in Diabetes*

By WILLIAM ALLAN, M.D., Charlotte, North Carolina

THE impression prevails that diabetes mellitus is in some degree hereditary. In discussing this matter Joslin¹ cites the frequency of a history of diabetes in grandparents, parents, uncles, aunts, and children as the group of relatives indicating hereditary tendencies, and the frequency of diabetes in siblings and cousins as indicating familial occurrence of diabetes. In two series of diabetic persons numbering 2,800 and 2,646 he finds the frequency of a history of diabetes in the "hereditary group" to be 15 per cent and 17 per cent respectively. His figures for the familial occurrence of diabetes in his two series are 7 per cent and 12 per cent respectively, while I secured a history of diabetes in sibs and cousins in 25 per cent of 143 diabetics. If his patients belonged to separate families the number of "hereditary group" relatives would be 108, 920 giving a diabetic incidence of approximately .8 per cent, which as he points out is not far from the incidence of diabetes in the general population at any time.

This method of evaluating the hereditary factor in diabetes seems unlikely to lead to anything definite. Would it not be better to take the incidence of diabetes in the general population, determine the expected incidence of diabetes in parents, siblings, and children? and compare these figures with our

actual findings? Joslin (page 131) estimates the incidence of declared and potential diabetes were inherited as a dominant unit character. Points in 100 per cent of instances: the actual finding of 10 per cent to 15 per cent of parental diabetes is so far from the expected incidence that it seems useless to consider further the inheritance of diabetes as a dominant character.

If diabetes were a unit recessive trait, Let D = gene for normal or non-diabetic condition

d = gene for diabetes

p = frequency of D

q = frequency of d

Then $p + q = 1$

The possible combinations of these factors are expressed by the equation $(p + q)^2 = 1$, and the chance association of genes is shown in figure 1.

	D (p)	d (q)
D (p)	DD (p^2)	Dd (pq)
d (q)	Dd (pq)	dd (q^2)

FIG. 1.

$$p^2 + 2pq = \text{non-diabetics}$$

$$q^2 = \text{diabetics}$$

$$q = \sqrt{\text{diabetics}}$$

Substituting Joslin's figure for the incidence of diabetes, 1.4%

$$q = \sqrt{.014} = .1185$$

$$p = 1 - q = .8815$$

Substituting the values of p and q in the foregoing equations

$$p^2 = \text{pure or homozygous non-diabetic} = 77.7 \text{ (DD)}$$

$$2pq = \text{hybrid or heterozygous non-diabetics} = 20.9 \text{ (Dd)}$$

$$q^2 = \text{diabetics} = 1.4 \text{ (dd)}$$

Within the non-diabetic group are the following ratios:

Homozygous non-diabetics = 78.8%

Heterozygous non-diabetics = 21.2%

The incidence in the general population if diabetes were recessive is shown in figure 2.

	DD .777	Dd .209	dd .014
DD .777	1 .6037	2 .1624	3 .0109
Dd .209	4 .1624	5 .0437	6 .0029
dd .014	7 .0109	8 .0029	9 .0002

1. DD×DD=DD	DD	DD	DD=60.37%
2. DD×Dd=DD	DD	Dd	Dd=16.24
3. DD×dd=Dd	Dd	Dd	Dd=1.09
4. Dd×DD=DD	DD	Dd	Dd=16.24
5. Dd×Dd=DD	Dd	Dd	dd=4.37
6. Dd×dd=Dd	Dd	dd	dd=.29
7. dd×DD=Dd	Dd	Dd	Dd=1.09
8. dd×Dd=Dd	Dd	dd	dd=.29
9. dd×dd=dd	dd	dd	dd=.02
100.00%			

FIG. 2

If diabetes were a recessive unit character with an incidence of 1.4%:

(1) One or both parents should have it in 22% of instances.

One-half of mating 6 = $Dd \times dd = .145$

One-half of mating 8 = $dd \times Dd = .145$

Mating 9 = $dd \times dd = .02$

Total incidence 1.4) .310(.22

In 143 cases I secured a history of diabetes in one parent in 17 instances, or 12%.

(2) Both parents should have it in 1.4%

Mating 9 = .02

1.4% = 1.4%

Total Inc. 1.4

Only twice have I encountered diabetes in both parents, but Joslin reports diabetes in both parents 42 times in 4675 cases, giving an incidence of .9%.

(3) One parent should have it in 20.7%

One-half mating 6 = $Dd \times dd = .145$

One-half mating 8 = $dd \times Dd = .145$

Total incidence 1.4) .290(.207

My figures show 12%.

(4) Neither parent should have it in 78%

One-fourth mating 5 = $Dd \times Dd = \frac{1}{4} \times 4.37$

1.4

In 88% of 143 cases I failed to obtain a diabetic history in either parent.

(5) If both parents have diabetes, then 100% of the children should have it. I have encountered diabetes in both husband and wife only twice; in one instance there were no children and in the other the number of diabetic children was unknown.

(6) If one parent has diabetes, 10.6% of the children should have it.

	DD .788	Dd .212		Dd	dd
dd	1	2	1 = Dd	Dd	Dd = 78.8%
1.00	.788	.212	2 = Dd	Dd	dd = 21.2
				dd	dd = 10.6%

I have not been able to find in the literature any figures on the percentage of children with diabetes when either one or both parents have it.

(7) If neither parent has diabetes, 1.125% of the children should have it.

	DD .788	Dd .212		DD	DD	DD	DD
DD	1	2	1 = DD	DD	DD	DD	DD = 62.10
.788	.621	.1670	2 = DD	DD	Dd	Dd = 16.70	
			3 = DD	DD	Dd	Dd = 16.70	
Dd	3	4	4 = DD	Dd	dd	dd = 4.50	
.212	.1670	.045					
				DD	Dd	dd	
				62.10%			
				8.35	8.35%		
				8.35	8.35		
				1.125	2.25	1.125%	

(8) If diabetes is recessive with an incidence of 1.4%, then 31.3% of the sibs of diabetics should have it.

One-fourth mating 5 = 1.09 : diabetic sibs 25% = .273
 One-half mating 6 = .145 : diabetic sibs 50% = .0725
 One-half mating 8 = .145 : diabetic sibs 50% = .0725
 Mating 9 = .02 : diabetic sibs 100% = .02

1.4 Total inc. 1.4) .4380 (31.29

I have only 24 separate families in which there was a history of diabetes in the sibs. These 24 diabetics had 36 sibs with diabetes, but the total number of sibs was not recorded. Taking 4.3 per cent as the average number of sibs there should thus be a total of 103 sibs in these 24 families, 36 or 35 per cent of whom have diabetes. As an actual fact in 15 of these families there were 101 children, that is, 86 sibs among whom there were 25 diabetic sibs which gives 29 per cent. But 143 diabetic patients would theoretically have 615 sibs and, as I secured a history of diabetes in only 36, this is only about 6 per cent.

(9) If diabetes is recessive with an incidence of 1.4%, then .98% of the sibs of non-diabetics should have it.

Three-fourths	mating 5 = 3.28	with diabetic sibs 25% = .82
One-half	mating 6 = .145	with diabetic sibs 50% = .0725
One-half	mating 8 = .145	with diabetic sibs 50% = .0725

Total incidence 98.6) .9650 (.98

I have no data on the frequency of diabetes in the sibs of non-diabetics.

SUMMARY

The data available at present are much too meager to warrant drawing any conclusions, but it seems possible that diabetes may be transmitted as a recessive unit character.

DISCUSSION

Since these notes were written about eighteen months ago, Wright³ has published an interesting discussion of "hereditary and familial diabetes mellitus", illustrated by nine charts of diabetic family pedigrees. He considers diabetes to be the product of two factors, an hereditary factor plus an acquired factor such as infection or obesity. Although none of his charts shows diabetes in more than two successive generations, he apparently follows Cammidge in believing that diabetes is sometimes a recessive trait (when severe in the young) and sometimes a dominant trait (when mild in the old).

Howard and Cammidge⁴ found that high fasting blood sugar in mice is transmitted as a unit recessive Mendelian trait, and Cammidge⁵ states "since the abnormality of carbohydrate metabolism giving rise to a high fasting blood sugar in animals is un-

doubtedly a recessive character, it is not unlikely that similar defects in the chemistry of the body of human beings may be transmitted in the same way, and that some forms at least of hyperglycemia and glycosuria, or the conditions predisposing to their development, may consequently run in families like a high fasting blood sugar in mice."

Cammidge discounts statistical studies and undertakes to illustrate the inheritance of human diabetes by family pedigrees of two or three generations, with half a dozen members in each generation, and promptly encounters the dilemma of pedigrees that correspond to both dominant and recessive traits, or to neither. In addition since his cases are not controlled by blood sugar reports, alimentary glycosuria, which is hereditary, may be a confusing element. Hence it seems wiser to stick to statistical studies, unless much more extensive family surveys can be made.

REFERENCES

- ¹JOHNS, R. P.: Treatment of diabetes mellitus, 1926, Lea & Febiger, Philadelphia, p. 142.
- ²WRIGHT, W.: Inheritance of diabetes, Arch. Int. Med., 1927, xlii, 500-506.
- ³WRIGHT, I. E.: Hereditary and familial diabetes mellitus, Ann. Jr. Med. Sci., Phil., 1928, 3:41-7.
- ⁴HOWARD, H. A. H., and CAMMIDGE, P. J.: Hyperglycemia as a Mendelian recessive character in mice, Jr. Genet., 1926, xvi, 357-392.
- ⁵CAMMIDGE, P. J.: Diabetes mellitus and heredity, Brit. Med. Jr., 1928, ii, 72-74.

Undulant Fever: A Fatal Case*†

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THERE have recently been numerous clinical publications on undulant fever. Kern,¹ in 1928, summarized the 36 abortus strain cases previously cited in the American literature and added two more. Simpson and Fraizer² in 1929, and Simpson³ in 1930, recorded the findings in a group of cases near Dayton, Ohio. In the latter year Giordano and Senenich⁴ reported a clinical analysis of 35 cases in Indiana. In the same year (1930) Hardy's⁵ extensive study in Iowa mentioned ten fatal cases, with gross and microscopic autopsy findings in two.

While the mortality rate has been placed by Hardy at 3 per cent, there are relatively infrequent references in the literature to fatal instances of the disease. The following case is reported because of the unusual opportunity to study the patient for a long time, and to follow him to the necropsy table.

CASE REPORT

W.J., aged 57, a farmer, who had lived in Michigan all his life, entered the University Hospital December 2, 1930, in the fifth month of an illness that had begun suddenly on July 6, 1930. The onset had been marked by cough, expectoration of large quantities

of tenacious sputum, chills and fever, drenching night-sweats, soon followed by generalized arthralgia, and by moderate dyspnea accompanying his usual activities. On July 15 a diagnosis of undulant fever had been made as a result of agglutination studies in a nearby laboratory (titer: Br. abortus 1:100). In the same laboratory one month later the titer was again significantly positive (Br. abortus 1:250).

Treatment with "convalescent serum" had produced a remission of symptoms for two weeks soon after the onset; then all symptoms had recurred and two more treatments with serum had afforded no improvement. In August, a series of rectal instillations of a "blue dye" had been of no avail. All symptoms had persisted until the time of admission to the hospital, although the arthralgia had become much less severe and the dyspnea more pronounced. The patient had been confined to bed since the exacerbation, about August 1, a period of four months. For three weeks before entrance there had been gradual swelling of the abdomen and slight edema of the ankles, accompanied by oliguria. The temperature had risen to 101° or 101.5° every afternoon since the onset.

The patient had been married for thirty-two years; there were no offspring. The remainder of the history was irrelevant. There had been no other illness with the exception of mild scarlatina in childhood. The man had been actively engaged in tending his farm, assisting in strenuous manual tasks until the sudden onset of this disease.

A possible source of infection existed in the patient's herd of cattle, three cows recently purchased having aborted. The patient stated that he drank raw milk only in hot coffee. No similar infection had occurred

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in any member of the patient's household. Agglutination of his wife's blood was negative. Subsequent bacteriological examination of milk samples in our laboratory failed to demonstrate brucella organisms.

The essential features of the physical examination were evidence of general weakness, moderate loss of flesh, ascites, and bilateral pretibial edema. The lungs showed only slight congestion at the right base. The heart was normal in position, size, and action; there was electrocardiographic evidence of small complexes and slight left ventricular preponderance. The palpable peripheral arteries were moderately sclerosed. The blood pressure was 114/72. A smooth liver edge could be felt 3.5 centimeters below the right costal margin. The spleen extended one finger's breadth below the ribs on the left.

The urine showed a trace of albumin at a few examinations. There were usually a few white blood cells in the sediment and occasionally a red corpuscle. A Lashmet-Newburgh² concentration test for kidney function gave a maximum value of 1.022, a reading slightly below normal for the method employed. The red blood cell count varied from 4,100,000 to 5,300,000, and the hemoglobin from 75 to 87 per cent on the Sahli scale. A leukopenia was a rather constant feature. The white cells averaged 4200 on ten examinations, with a range between 3200 and 7000. A terminal rise to 17,000 occurred. The average polymorphonuclear percentage was 53, and there was a slight relative lymphocytosis, with an average of 42 per cent. The character of cells and platelets was normal at all times.

The stool was normal. The sputum was clear, of unaltered consistency, and contained no organisms. Two examinations of the ascitic fluid showed it to be colorless, clear, neutral to litmus, with specific gravity of 1.007 to 1.010, and containing an average of 700 cells per cubic millimeter, chiefly lymphocytes. There were also mesothelial cells, but no leukocytes.

The Rastky test on the blood serum was negative. Blood nitrogen, nitrogen and creatinine, and urea on the day after admission were 14.4, 1.4, and 0.4 mgm. per 100 ml. respectively. Blood

grams per cent, and 6 milligrams per 1000 c.c. (indirect reaction).

Four blood cultures were negative. Cultures of the urine and ascitic fluid, and of the stool by the technic of Amoss and Poston⁷ gave no growth.

Agglutination values were as indicated in the table. The titer remained at a significantly high level throughout the period of observation, being always highest for the melitensis strain. The variation between melitensis agglutination and that for abortus, while usually a difference of only one dilution, was occasionally more marked, a finding of interest which is at variance with the reported studies of some authors.* The absence of any cross-agglutination with members of the typhoid group is worthy of mention. The presence of agglutinins for brucella organisms in the ascitic fluid confirms the previously recognized fact that secretions from the serous cavities can agglutinate various bacteria in the presence of infection with those bacteria.

The clinical course of the disease during 133 days in the hospital is shown on the chart. The temperature was of intermittent character, with several short apyrexial periods. These give to the curve an irregularly undulant appearance, somewhat like some of the temperature types illustrated in the reports of the Mediterranean Fever Commission in 1905.⁸ Similar findings have been recorded by Craig,⁹ Giordano,⁴ and other writers in their more chronic cases.

The pulse and respiration showed ranges generally proportional to the temperature, although at times the heart rate was relatively slow.

Loss of weight was progressive, associated with increasing weakness. The cough and sputum disappeared soon after admission and under maintenance doses of digitalis there was no longer dyspnea at bed rest. The use of a neutral diet with ammonium chloride,

*Additional unpublished data are at hand which show a similar variation in undulant fever cases. In these, agglutination for *Brucella melitensis* was also studied, and likewise showed no constancy in values in relationship to the others.

and, in addition, the intravenous administration of Salyrgan failed to control the accumulation of ascites, necessitating several paracenteses, as illustrated.

Two courses of brucella vaccine were given according to the method recommended by Simpson.^{3,10} The second saline suspension contained twice as many brucella organisms (*abortus* and *melitensis* strains) as the first. Although no specific *intradermal* test was tried with these preparations, which were given subcutaneously, after the first injection with the stronger solution there appeared a localized red area which became indurated, in a manner entirely comparable

was flabby, with a moderate excess of overlying fat. Microscopically, it showed brown atrophy, and slight endocardial sclerosis with fibrosis extending into the myocardium. Bilateral basal confluent lobular pneumonia was evident as were also chronic passive congestion and chronic edema of the lungs. The liver was atrophic, with moderately sharp and pointed edges. The capsule was of normal thickness, and showed numerous small grayish nodules over its surface. The organ cut with increased resistance. There was marked increase of connective tissue, chiefly perilobular in distribution. Occasional yellowish-gray areas of lipid deposit

DATE	BLOOD				ASCITES			URINE		
	BR ABORT	BR MELIT	B TULAR	TYPH GR	BR ABORT	BR MELIT	TYPH GR	BR ABORT	BR MELIT	TYPH GR
12-2-30	1320	1640	—	NEG						
12-4-30	1640	11280	—	NEG	180	1160	NEG			
12-5-30	1320	1640	—	NEG						
12-14-30								NEG	NEG	NEG
12-15-30					140	180	NEG			
12-26-30	1160	1320	—	NEG						
1-6-31	1160	1160	NEG	—						
1-19-31					180	1160	—			
3-10-31	180	1320	—	—						
3-13-31					120	180	—			
3-30-31					140	180	—			
4-7-31	1160	1320	—	—						
4-14-31	180	1320	—	—	140	1160	—			
POST-MORTEM										

FIG. 1. Agglutinin values. Typhoid Group includes *B. Typhosus*, *B. Paratyphosus A.*, and *B. Paratyphosus B.*

to the reaction obtained with saline intradermal brucella antigens.

No appreciable result was obtained by either course of vaccine therapy. The clinical progression was steadily downward. Erysipelas of the face developed about a week before death, but cleared completely under treatment with continuous magnesium sulfate dressings. There was evidence of terminal pneumonia in both lower lobes. Exitus occurred on April 13, 1931, the 283rd day of disease.

The significant autopsy findings were as follows: 3400 c.c. of ascitic fluid were recovered and 200 c.c. of effusion were present in each pleural cavity. The pericardial sac was under slightly increased tension due to the presence of 150 c.c. of fluid. The heart

and moderate congestion were seen. Under the microscope, chronic passive congestion, patchy fatty infiltration, and irregularly distributed chronic parenchymatous hepatitis of the type of atrophic cirrhosis were distinguished. Chronic interstitial pancreatitis was noted. There was atrophy, passive congestion, and parenchymatous degeneration of all organs.

The spleen and testes were of prime interest, the former because of its important place in all references since the earliest writings about undulant fever, the latter particularly because of its association as a complication in the disease, orchitis being prominently mentioned by Simpson,³ Hardy,⁵ and others.

Grossly, there were diffusely scattered pin-

in any member of the patient's household. Agglutination of his wife's blood was negative. Subsequent bacteriological examination of milk samples in our laboratory failed to demonstrate brucella organisms.

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The Kahn test on the blood serum was negative. Blood non-protein nitrogen and blood bilirubin values the day after admission to the hospital were respectively 34.2 milli-

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The pulse and respiration showed ranges generally proportional to the temperature, although at times the heart rate was relatively slow.

Loss of weight was progressive, associated with increasing weakness. The cough and sputum disappeared soon after admission and under maintenance doses of digitalis there was no longer dyspnea at bed rest. The use of a neutral diet with ammonium chloride,

*Additional unpublished data are at hand which show a similar variation in undulant fever cases. In these, agglutination for *Brucella suis* was also studied, and this titer likewise showed no constancy in value nor in relationship to the others.

and, in addition, the intravenous administration of Salyrgan failed to control the accumulation of ascites, necessitating several paracenteses, as illustrated.

Two courses of brucella vaccine were given according to the method recommended by Simpson.^{3,10} The second saline suspension contained twice as many brucella organisms (abortus and melitensis strains) as the first. Although no specific *intra*dermal test was tried with these preparations, which were given subcutaneously, after the first injection with the stronger solution there appeared a localized red area which became indurated, in a manner entirely comparable

was flabby, with a moderate excess of overlying fat. Microscopically, it showed brown atrophy, and slight endocardial sclerosis with fibrosis extending into the myocardium. Bilateral basal confluent lobular pneumonia was evident as were also chronic passive congestion and chronic edema of the lungs. The liver was atrophic, with moderately sharp and pointed edges. The capsule was of normal thickness, and showed numerous small grayish nodules over its surface. The organ cut with increased resistance. There was marked increase of connective tissue, chiefly perilobular in distribution. Occasional yellowish-gray areas of lipid deposit

DATE	BLOOD				ASCITES			URINE		
	BR ABORT	BR MELIT	B TULAR	TYPH GR	BR ABORT	BR MELIT	TYPH GR	BR ABORT	BR MELIT	TYPH GR
12-2-30	1320	1640	—	NEG						
12-4-30	1640	11280	—	NEG	180	1160	NEG			
12-5-30	1320	1640	—	NEG						
12-14-30								NEG	NEG	NEG
12-15-30					140	180	NEG			
12-26-30	1160	1320	—	NEG						
1-6-31	1160	1160	NEG	—						
1-19-31					180	1160	—			
3-10-31	180	1320	—	—						
3-13-31					120	180	—			
3-30-31					140	180	—			
4-7-31	1160	1320	—	—						
4-14-31	180	1320	—	—	140	1160	—			
POST-MORTEM										

FIG. 1. Agglutinin values. Typhoid Group includes *B. Typhosus*, *B. Paratyphosus A.*, and *B. Paratyphosus B.*

to the reaction obtained with saline intra-dermal brucella antigens.

No appreciable result was obtained by either course of vaccine therapy. The clinical progression was steadily downward. Erysipelas of the face developed about a week before death, but cleared completely under treatment with continuous magnesium sulfate dressings. There was evidence of terminal pneumonia in both lower lobes. Exitus occurred on April 13, 1931, the 283rd day of disease.

The significant autopsy findings were as follows: 3400 c.c. of ascitic fluid were recovered and 200 c.c. of effusion were present in each pleural cavity. The pericardial sac was under slightly increased tension due to the presence of 150 c.c. of fluid. The heart

and moderate congestion were seen. Under the microscope, chronic passive congestion, patchy fatty infiltration, and irregularly distributed chronic parenchymatous hepatitis of the type of atrophic cirrhosis were distinguished. Chronic interstitial pancreatitis was noted. There was atrophy, passive congestion, and parenchymatous degeneration of all organs.

The spleen and testes were of prime interest, the former because of its important place in all references since the earliest writings about undulant fever, the latter particularly because of its association as a complication in the disease, orchitis being prominently mentioned by Simpson,² Hardy,⁵ and others.

Grossly, there were diffusely scattered pin-

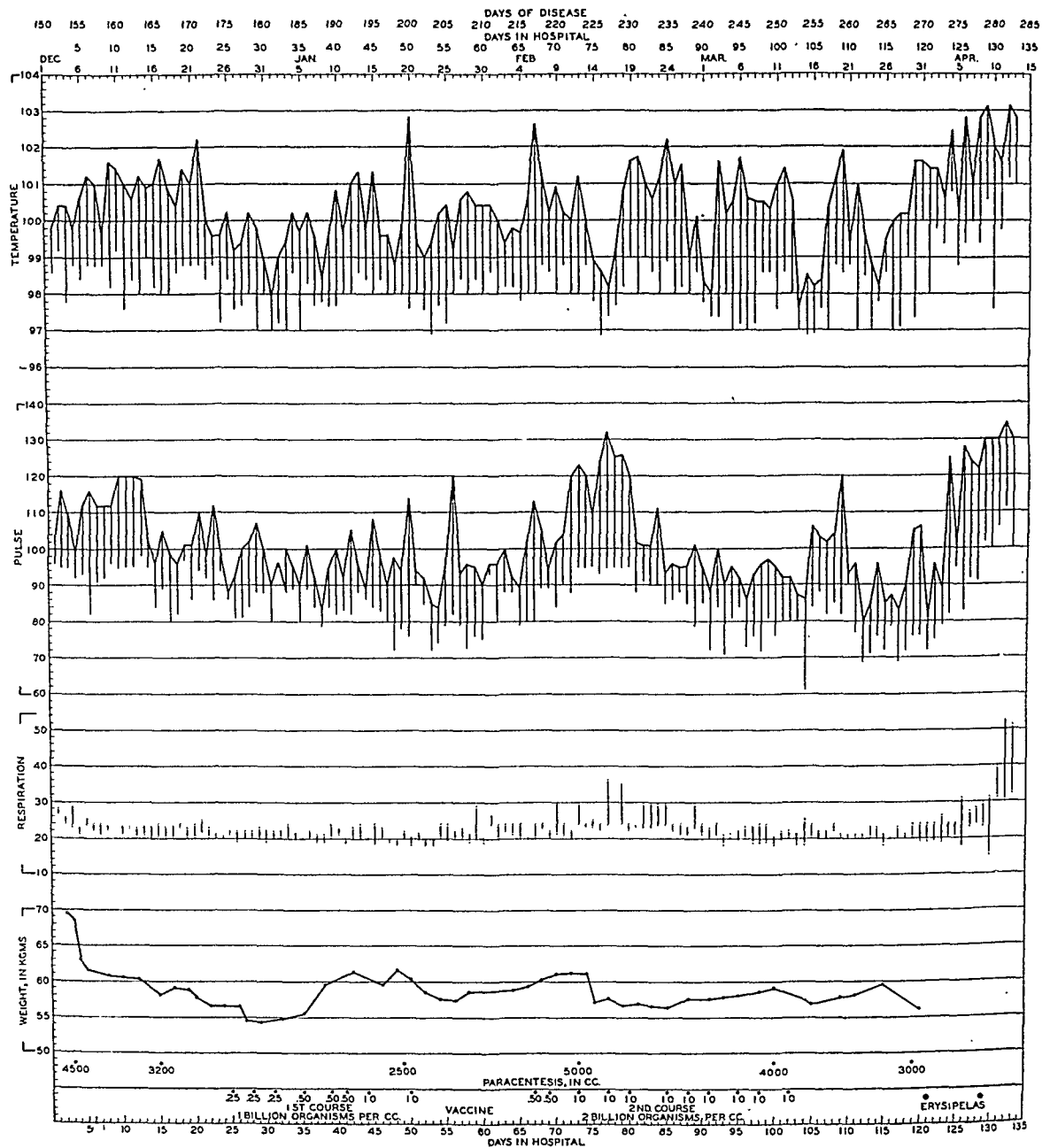


FIG. 2. Course of the disease during hospitalization. Each vertical column represents one day, with range from minimum to maximum for temperature, pulse, and respiration.

head sized, reddish, translucent nodules on the splenic surface, somewhat resembling tubercles. These proved microscopically to be localized areas of perisplenitis with hyaline change. The spleen was slightly enlarged with rounded edges. The capsule was thickened. There was lymphoid hyperplasia throughout. The sinuses were dilated and contained numerous macrophages in which red blood cells and blood pigment were engulfed. A few multinucleate giant cells were also present in the sinuses.

The testes revealed complete aspermatogenesis, with evidence of active interstitial orchitis, and scattered areas of fibroid atrophy. Vacuolar degeneration of the epithelium was noted. The prostate and seminal vesicles were normal.

DISCUSSION

Whether these pathological changes may be considered specific of undulant fever is open to question. The patient

died because of arteriosclerotic heart disease and cirrhosis of the liver. It is unlikely, however, that without the concomitant undulant fever impaired function of these organs would have been manifested when it was, or that death would have ensued when it did. On the other hand, it is entirely possible that without the hepatic damage and cardiac weakness the undulant fever would have run a shorter and more favorable course.

The precedent history of sterility does not permit an opinion that the aspermatogenesis was due to undulant fever. The active orchitis, however,

can be more justifiably related to this disease.

It is interesting that both of Hardy's⁵ cases showed hepatic damage and cardiac involvement at autopsy after a rather chronic course of illness.

In the present instance it seems at least highly suggestive, in view of the previous vigorous health, that the visceral damage resulted from the prolonged brucella infection.

SUMMARY

A prolonged fatal case of undulant fever is presented and discussed with reference to its clinical, laboratory, and pathological considerations.

BIBLIOGRAPHY

¹KERN, R. A.: Clinical aspects of *Brucella Melitensis* variety *abortus* infection in man; report of first cases recognized in Pennsylvania, *Am. Jr. Med. Sci.*, 1928, clxxvi, 405-430.

²SIMPSON, W. M., and FRAIZER, E.: Undulant fever; report of sixty-three cases occurring in and about Dayton, Ohio, *Jr. Am. Med. Assoc.*, 1929, xciii, 1958-1963.

³SIMPSON, W. M.: Undulant fever (*Brucelliasis*); a clinicopathologic study of ninety cases occurring in and about Dayton, Ohio, *ANN. INT. MED.*, 1930, iv, 238-259.

⁴GIORDANO, A. S., and SENSENICH, R. L.: *Brucella abortus* infection in man; clinical analysis of thirty-five cases, *Jr. Lab. and Clin. Med.*, 1930, xv, 421-436.

⁵HARDY, A. V., et al: Undulant fever, with

special reference to a study of brucella infection in Iowa, *Nat. Inst. of Health Bull. No. 158*, Dec. 1930.

⁶LASHMET, F. H., and NEWBURGH, L. H.: Specific gravity of urine as a test of kidney function, *Jr. Am. Med. Assoc.*, 1930, xciv, 1883-1885.

⁷AMOSS, H. L., and POSTON, M. A.: Undulant (Malta) fever; isolation of the *Brucella* organism from stools, *Jr. Am. Med. Assoc.*, 1929, xciii, 170-171.

⁸Report on Mediterranean Fever, *Proc. Roy. Soc. Med.*, 1905, Part I. pp. 30, 32, 33; Part II, pp. 59, 61.

⁹CRAIG, C. F.: The symptomatology and diagnosis of Malta fever, with the report of additional cases, *Internat. Clinics, Phila.*, 15th s., 1906, iv, 89-115.

¹⁰SIMPSON, W. M.: Personal communication.

Subacute Yellow Atrophy of the Liver Following Ingestion of Cinchophen and Allied Compounds*†

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CASE REPORT

CINCHOPHEN was first introduced to therapeutics in 1908 by Nicolaier and Dohrn for the treatment of gout. Since then its use has been extended to arthritis in general and as an analgesic. Various closely allied chemical compounds and derivatives have been brought out from time to time until now there are many similar drugs on the market, and with the multiplicity of trade names it is doubtful whether persons using or prescribing them are fully acquainted with the toxicity which they possess. Rabinowitz¹ has listed twenty in this group of remedies, and there are probably others.

The toxicity of these preparations has obtained considerable notoriety in the past few years. The occurrence of fatalities and of less serious complications has been so frequent that recently it has drawn editorial comment in the *Journal of the American Medical Association*.² The data of carefully studied cases of such poisoning should be published in order to stimulate the development of proper safeguards.

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The case we wish to describe is that of a feeble white woman, aged 68 years. For many years she had been troubled with arthritis, involving especially the shoulders and hands. She had used many different remedies, the names of which could not be learned. It was noted by the family that for the two years prior to death, she had been growing weaker, was unable to accomplish her housework in a satisfactory manner, and had nervous manifestations, such as incoördinated twitchings of various muscle groups. She had lost from ten to fifteen pounds in the past year, although her appetite was good and she ate well without complaining of gastrointestinal symptoms.

During the three months she had been under our observation her chief symptoms were extreme weakness, slight incoördination of muscular movements accompanied by twitching, insomnia, arthritis of shoulders and hands, and loss of weight. Examination of heart, lungs, and kidneys showed nothing abnormal.

She was given occasional doses of luminal ($\frac{1}{2}$ gr.) for nervousness and insomnia with good results. Occasionally she would take two or three teaspoonfuls of whiskey in warm milk at bedtime. For arthritis she was given cinchophen intermittently—averaging two tablets daily for a few days and then stopping for a few days. She took about 35 tablets (262.5 grains) in the last two months. She was also given at other times oxyl-iodide, about two capsules daily for a few days, the drug then being discon-

tinued for several days. Of this she took about 25 capsules (75 grains). It was learned that prior to coming under our observation she had used atophan for various periods, the amounts or rate not being known.

About two months previous to death she had two acute spells of chills and fever, lasting about one and a half days each, about two weeks apart. The temperature reached 101°-102°. The symptoms each time cleared up entirely on rest in bed for a day. Leukocyte counts were within normal limits on both occasions.

On March 31, jaundice was noted. About two days before this she had taken one capsule of oxyd-iodide, but this had caused nausea, and no more of the drug had been used. The jaundice rapidly became very intense. There was no apparent diminution in the intensity of the jaundice, either clinically or by observation of urine. The urine showed albumin, hyaline, and finely granular casts, and an occasional red cell. Bile was present.

The jaundice continued for about four weeks, until death intervened. The stools were clay colored for the most part, although occasionally a small amount of bile coloration could be seen. About a week before death, toxic symptoms became more prominent. Her speech was somewhat thick, and she was quite drowsy, and finally two days before her death she lapsed into a semicomatose condition from which she would arouse only momentarily. The forcing of fluids was followed by edema of the legs, but this subsided somewhat when she was put on a Karrell diet. Toward the end there was marked tympanites, but ascites was not noted until about two days before death. Her temperature was normal throughout this later period. It is worthy of note that after the appearance of jaundice she had no subjective symptoms of arthritis.

Necropsy was performed one and a half hours post mortem.

Anatomical Diagnosis: Subacute yellow atrophy of the liver; jaundice; dilatation of the mesenteric veins; bronchopneumonia.

The body is fairly well developed and nourished, 61 inches long. There is slight edema of the ankles. The skin is markedly jaundiced and the sclerae are deep yellow.

No teeth are present. There is a small pigmented mole at the right external canthus and numerous small pigmented moles on the chest and back. Varicosities of the veins of both legs are present.

The abdominal fat is deep yellow, 3 cms. thick. Throughout the body the tissues are markedly jaundiced.

Peritoneal Cavity: Contains about 400 c.c. of clear, bile-stained fluid. There are firm adhesions about the spleen, gall-bladder, and appendix. In the area of the gall-bladder and the under surface of the liver the tissues are very edematous.

Pericardial Cavity: Contains a normal amount of bile-stained fluid.

Heart: Normal in size. Pericardial fat is normal in amount but is deeply bile-stained. The coronary arteries are very slightly thickened and on section the myocardium presents numerous grey plaques and streaks. The endocardium is smooth and glistening throughout. The edges of the mitral valve are slightly thickened.

Lungs: The external surface of the right lung is mottled grey. The lower lobe is slightly more firm and deeper in color. There is a scar at the apex. On section there is congestion and edema of the lower lobe. The left lung resembles the right.

Spleen: Is light grey and presents several irregular, deeply pigmented areas. On section the cut surface is firm and deep red.

Gastrointestinal Tract: Normal except for a few small areas of injection in the mucosa.

Pancreas: Is normal but the tissues about the pancreas present marked edema and bile staining.

Liver: Is small, firm, and nodular. Weight 650 gms. The external surface is bile-stained and marked by numerous small nodules. It cuts with considerable resistance, and the cut surface is bile-stained, hard and fibrous and irregularly lobulated. In the upper posterior part of the right lobe is an area about 8 by 5 cms., smooth and practically normal. The middle of the left lobe on its anterior surface is also quite smooth and lies below the level of the nodular tissue. The veins of the falciform ligament are markedly dilated.

Gall-Bladder and Ducts: There is much

edema and bile staining in the tissues about the gall-bladder. The ducts are patent but there is a very little bile in the gall-bladder. The mucosa of the gall-bladder is grossly normal. No stones are found.

Kidneys: Right is of normal size. There are numerous small subcortical cysts. On section the cut surface is markedly bile-stained. The cortex averages 5 mms. and

Lungs: Scattered foci of acute pneumonia.

Spleen: Normal.

Pancreas: Normal except for a rare focus of acute interstitial pancreatitis.

Adrenal: Normal.

Stomach: Normal.

Duodenum and Jejunum: Perivascular lymphoid cells and eosinophiles are seen in

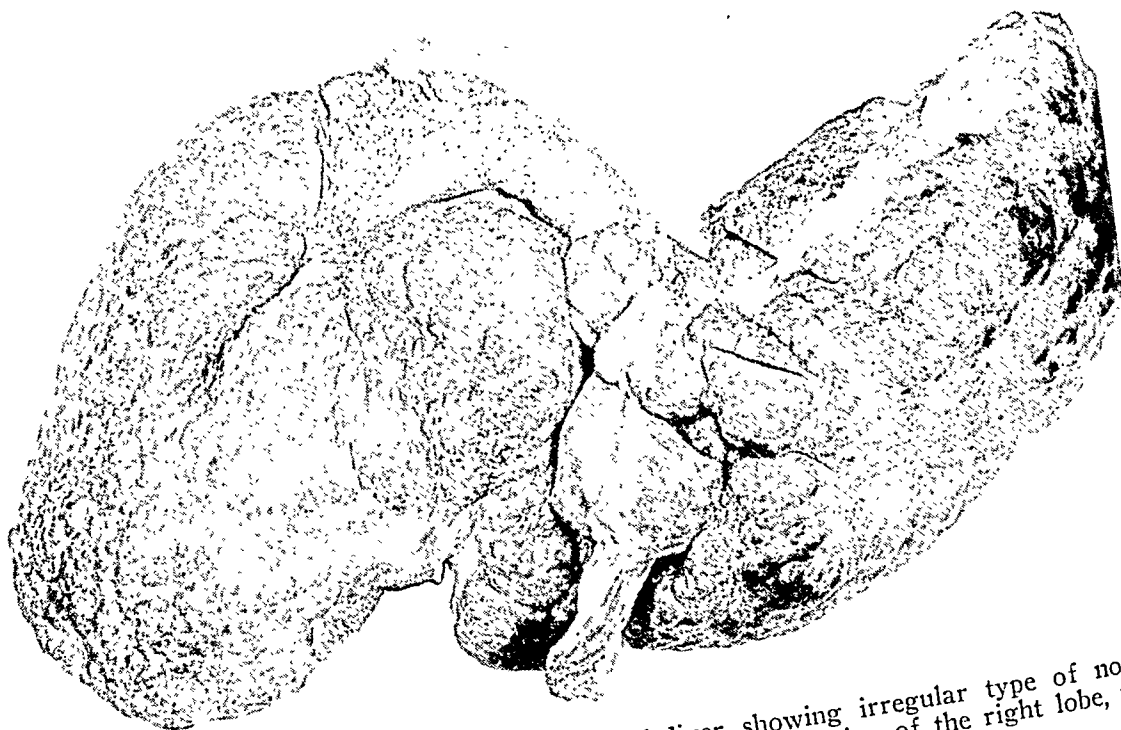


FIG. 1. Photograph of anterior surface of liver showing irregular type of nodular cirrhosis following destruction of most of parenchyma. A portion of the right lobe, upper zone, is practically uninvolved.

the capsule strips with ease, leaving a smooth surface marked by small cysts. The left kidney resembles the right. The vessels and ureters are normal.

Adrenals: Normal.

Bladder: Is filled with dirty mud-colored urine. The mucosa is slightly injected.

Genitalia: Cervix is senile in type, endometrium is hemorrhagic and there is a small leiomyoma in the posterior wall.

Aorta: Presents numerous atheromatous plaques in the abdominal portion.

MICROSCOPIC EXAMINATION

Heart: A section of left ventricle is normal.

the muscularis and beneath a thickened serosa. No ulceration.

Kidneys: Many bile-stained hyaline and granular casts in the cortex. Glomeruli slightly thickened.

Uterus: Many large hemorrhages in endometrium and upper layer of myometrium which also shows much myofibrosis.

Ovary: Senile type.

Gall-Bladder: Marked chronic inflammation of mucosa and submucosa with heteroplasia of mucosal epithelium.

Liver: Widespread destruction of lobules with loss of architecture. Many sections contain no parenchyma but only proliferating bile ducts, mononuclear cells, stroma,

and blood vessels. Certain parts show regenerating liver cells in pseudo-lobule formation. The bile canaliculi are dilated with bile thrombi. The capsule of the liver is much wrinkled due to loss of substance beneath. The picture is typical of subacute "yellow atrophy" or necrosis of toxic origin with some repair.

2-phenyl-quinolin-4-carboxylic acid. They prepared it by warming together pyrrolic acid, benzaldehyde and anilin in alcoholic solution.

Action. It stimulates the kidneys in such a way as to have a selective effect on the excretion of uric acid, which is

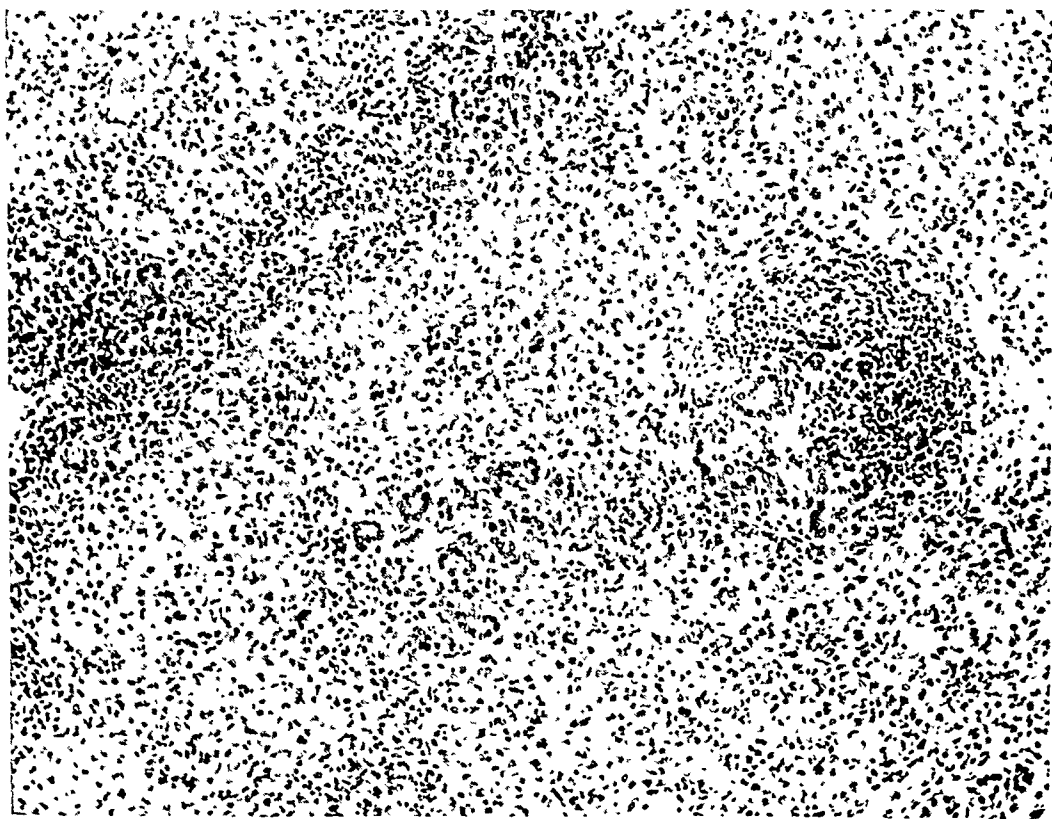


FIG. 2. Photomicrograph showing the loss of liver parenchyma, infiltration of lymphoid cells and proliferation of bile duct epithelium.

Microscopic Diagnosis: Subacute yellow atrophy of liver; chronic cholecystitis; acute pancreatitis; acute pneumonitis; endometrial hemorrhage.

DISCUSSION

Cinchophen. Cinchophen is phenyl-quinolin-carboxylic acid. It was introduced in therapeutics under the proprietary name "atophan" and is derived from quinolin carboxylic acid. Doebner and Giesecke in 1887 described

increased considerably. The amount of ammonia and of total nitrogen in the urine is slightly increased during the action of cinchophen. Cinchophen does not increase the leukocytes, purin bases or the phosphoric acid. There is no evidence of increased formation of uric acid nor of any effect on deposited urates.

The above two paragraphs are taken from *New and Nonofficial Rem-*

edies, 1924 edition, published by the American Medical Association.

The clinical use of cinchophen has been based largely upon the fact that there is an increase in uric acid output after its administration. While the mechanism of this effect is not entirely clear there seems to be a selective action on renal epithelium since a diuresis is also produced. It has become, next to diet, the chief weapon in the treatment of gout. The drug and its derivatives have also an important analgesic effect and are antipyretics as well, features likely to attract clinical interest towards any therapeutic agent.

According to Rabinowitz¹ toxic jaundice and hepatolysis may result not only from atophan (cinchophen), but also from atophanyl and diiodoatophan. Atophanyl is a combination of the sodium salt of atophan and salicylic acid, while diiodoatophan contains 50.7 per cent iodine and has been used in Austria and Germany for cholecystography.

The toxic action of cinchophen has been thought due to the quinolin nucleus, consisting of the benzol and pyridin rings which yield the toxic, free benzol ring. Most individuals, fortunately, are not susceptible to the toxic effect of the drug. It is undoubtedly true that toxic jaundice will result only in the case of individual idiosyncrasy, but the fact remains that in spite of supposedly careful use of these compounds fatalities do occur. It is also true that serious symptoms may develop after withdrawal of the offending drug. Contraindications to use, such as nausea, vomiting or gastrointestinal symptoms, may not be

present at all or come so late that they cannot be used as criteria of toxicity. Because of these facts cinchophen and its derivatives must be regarded as sources of danger and it would seem best to restrict their use when possible in favor of drugs which are less toxic.

Great importance must undoubtedly be given to the amount of glycogen in the liver cells at the time of cinchophen administration. There is undoubtedly a greater tendency to liver degeneration where there is malnutrition and a decrease in the glycogen content of the liver cells. As a result of this depletion, intoxications tend more readily to cause degeneration of the liver cells. Especially predisposed are alcoholics, pregnant women, and those who in the past have suffered from liver diseases associated with jaundice. It is important to remember that cases of chronic liver atrophy may suddenly present a picture of acute yellow atrophy, leading rapidly to death.

The dose or the duration of use of the drug will vary in individual instances—one developing toxic jaundice after as small a dose as 7 grains, others having a tolerance of several thousand grains taken during a period of years before intoxication occurs.

In 1922, Schroeder² described jaundice resulting from the use of cinchophen and published a review of seventeen cases. Since then the literature has shown many examples of fatalities from its use.

In 1929, Reichle⁴ described two cases of toxic cirrhosis due to cinchophen resulting in death, and gave an excellent review of the literature since

1922. He found 47 reports of poisoning with 10 deaths.

Hitzenberger⁵ cites the case of a young woman who died 10 days after diiodoatophan, administered for cholecystography. She had suffered from diabetes insipidus and occasional febrile attacks. A slight tenderness under the ribs suggested the possibility of gall-bladder disease, and cholecystography was undertaken.

Singer⁶ also reported the case of a 50-year-old woman whose death took place after the use of diiodoatophan for cholecystography. Definite jaundice occurred the following day.

Langdon-Brown⁷ observed fatalities after the use of atophan for rheumatism and stated that he knew of several others.

Anderson and Teter⁸ reported a fatality in a woman of 48 years who had been taking oxyl-iodide capsules for arthritis.

Stacy and Vanzant⁹ recorded the case of a woman of 52 years who took from one to three tablets of cinchophen daily for pain. She finally discontinued its use because of nausea and vomiting, but evidently too late, as she died one week later from acute yellow atrophy of the liver.

Rabinowitz¹⁰ has recently reported seven additional cases of cinchophen poisoning, four of which were fatal. He quoted Dr. Leo Kessel as having seen thirteen cases of atophan poisoning. From conversations with various practitioners in eastern New York we have concluded that in the use of this group of drugs untoward symptoms are very frequently observed, and that there are many unreported fatalities.

A striking fact is the high propor-

tion of fatal cases in women. Twelve of fourteen deaths occurred in females. The ages vary from 20 to 63. The influence of pregnancy and its frequent toxemias on the liver, the higher incidence of gall tract disease in women, and the more general tendency in women to disturbances of metabolism in later adult life, may all be factors in producing this sex preponderance.

The incidence of diffuse toxic necrosis of the liver—or, as it is more commonly but less properly called, acute yellow atrophy—has apparently increased in recent years, a fact attributed to the increasing use of various cyclic organic compounds, among which is the group concerned in our case.

The etiology is quite unknown but probably there is no specific cause since various forms of intoxication may closely simulate acute yellow atrophy, i.e., puerperal eclampsia, streptococcus septicemia, also poisoning with phosphorus, arsenic, nitrophenols, and even mushrooms. It is probably true, as Wells and Bassoe¹¹ state, that *any poison which does not directly cause death, but which causes a severe injury to the liver cells without at the same time destroying the autolytic enzymes, so that the cells die and undergo rapid autolysis, may produce a condition identical with or similar to acute yellow atrophy.*

Intracellular oxidations are probably affected in diffuse toxic necrosis, although fatty infiltration is more evident in the liver of phosphorus, chloroform and other poisonings. The fatty change is taken to be evidence of inhibition or destruction of oxidizing enzymes, the autolytic enzymes

being left free to act.¹² The ability of sugar to protect the liver from poisons such as phosphorus and chloroform seems to depend on its furnishing easily oxidizable material to cells with lessened oxidative capacity (Simonds¹³). Ervin,¹⁴ however, regards the protective action of carbohydrate as due to the liver glycogen which protects the protein-fat emulsion of the protoplasm from the action of acids. Nevertheless with the liver destruction carbohydrate tolerance is reduced (Bodansky¹⁵).

Stewart, Vining and Bibby¹⁶ emphasize the fact that acute yellow atrophy occurs more often after poisoning with picric acid, trinitrotoluene, dinitrobenzene, and aromatic arsenicals, and since the benzol ring is the only common component in these compounds, and is also present in cinchophen, its responsibility is strongly suggested.

In the literature dealing with poisonings of various kinds the word idiosyncrasy is frequently encountered. This term implies that a person has some peculiar constitutional susceptibility to the substance in question, a condition incapable of more concrete definition and hence probably covering a multiplicity of contributing factors. Minute analysis of clinical and pathological data may often give a more objective basis for the toxic state. In our case, for instance, at necropsy a very marked chronic cholecystitis was present although no gall-stones were found. This condition may have been present for years and possibly was responsible for the use of drugs for the "shoulder" pains which she had experienced. There is no definite evidence that gall-bladder disease per se

affects liver function, but it is conceivable that such contiguous lesions may render the liver less resistant to toxins which have an affinity for it.

Cinchophen or atophan and its related compounds are sold in most drug stores. Theoretically they are supposed to be procurable only by prescription but it is quite feasible for any one to purchase them without a physician's written order. This of course leaves open the possibility of abuse of the drug by the laity, especially since the bottles in which the powders or tablets are put up have no precautions printed on the labels. The physician is probably to blame in large measure for most cases of cinchophen poisoning since he is the proper person to warn his patients about the dangers of any form of medication he prescribes.

One manufacturer of this group of remedies gives ample warning to the profession about their contraindications. In a pamphlet¹⁷ sent out to physicians at regular intervals by this company the following cautions are given: "Discretion should be exercised in the use of this drug with individuals suffering from hepatic and biliary dysfunction, especially as it is evidenced in the elderly and poorly nourished patient; yet, if progressive degeneration of these organs is neither known to be present nor reasonably to be suspected, clinical observers believe that this form of medication need not be withheld, more especially if a diet rich in carbohydrates be provided and maintained paralleling the treatment. The use of oxyl-iodide compound is not recommended during pregnancy or for alcoholics. The drug should be at

once discontinued if any of the following symptoms are observed: loss of appetite, nausea, vomiting, tenderness over the liver or in the gall-bladder region, ictteroid tint to the sclera or skin, urticarial rash, itching of the skin, swelling of the lips, tongue or face. The appearance of albumin, casts, or bile in the urine should be an indication for the interruption of the administration of the drug."

It would seem that the above constitutes a very genuine effort upon the part of the manufacturer to make the physician realize the dangers of the cinchophenic compounds. Certainly it behooves the latter to acquaint himself thoroughly with their powers for evil before prescribing them for his patients. The dispenser, on the other hand, should be required to indicate on the labels of the containers the dangers of the unguided use of the contents.

SUMMARY ·

1. Cinchophen or atophan and its related compounds are capable in susceptible individuals of causing toxic symptoms which may eventuate in the so-called yellow atrophy of the liver.

2. A case is reported of subacute yellow atrophy in a woman aged 68 years, who in the previous two months had taken for arthritic pains about 263 grains of cinchophen and 75 grains of oxyl-iodide-phenylcinchoninic acid.

3. The benzol ring is a common component of this group of remedies and its responsibility for the toxicosis is strongly suggested.

4. Physicians prescribing these drugs should become familiar with their dangers and warn patients against using them without direction.

5. A large majority of the cases of poisoning occur in women.

6. In our case a concomitant cholecystitis of marked degree was present.

REFERENCES

- ¹RABINOWITZ, M. A.: Toxic hepatitis and hepatolysis following use of atophan, *Med. Clin. N. Am.*, 1928, xi, 1025-1041.
- ²EDITORIAL: Atrophy of the liver due to cinchophen preparations, *Jr. Am. Med. Assoc.*, 1930, xcv, 345.
- ³SCHROEDER, K.: Cases of cinchophen poisoning, *Ugesk. f. Laeger, Kopenh.*, 1922, lxxxiv, 1141-1152.
- ⁴REICHLE, H. S.: Toxic cirrhosis of liver due to cinchophen, *Arch. Int. Med.*, 1929, xlv, 281-288.
- ⁵HITZENBERGER, K.: *Verhandl. d. Gesellschaft der Aerzte in Wien.*, *Wien. klin. Wchnschr.*, 1927, xl, 205-207.
- ⁶SINGER, S.: Discussion of paper by G. Schwarz, *Schwerer Ikterus Nach Bilopten*, *Wien. klin. Wchnschr.*, 1927, xl, 238-239.
- ⁷LANGDON-BROWN, W.: Atophan derivatives in rheumatism, *Brit. Med. Jr.*, 1926, ii, 37.
- ⁸ANDERSON, S. D., and TETER, D. P.: Acute yellow atrophy of liver following administration of oxyl iodide, *Jr. Am. Med. Assoc.*, 1929, xciii, 93-95.
- ⁹STACY, L. J., and VANZANT, F. R.: Poisoning from cinchophen, *Minn. Med.*, 1930, xliii, 327-328.
- ¹⁰RABINOWITZ, M. A.: Atrophy of liver due to cinchophen preparations, *Jr. Am. Med. Assoc.*, 1930, xcv, 1228-1233.
- ¹¹WELLS, H. G., and BASSOE, P.: Acute yellow atrophy of the liver, *Jr. Am. Med. Assoc.*, 1905, xlv, 685-692.
- ¹²WELLS, H. G.: Delayed chloroform poisoning and allied conditions, *Jr. Am. Med. Assoc.*, 1906, xlvi, 341-343.

- ¹³SIMONDS, J. P.: Mechanism of protective action of carbohydrate diet in phosphorus and chloroform poisoning, *Arch. Int. Med.*, 1919, xxiii, 362-379.
- ¹⁴ERVIN, D. M.: Relation of glycogen to pathologic changes in pancreatic diabetes, *Jr. Lab. and Clin. Med.*, 1919, v, 146-153.
- ¹⁵BODANSKY, M.: Effect of chloroform and phosphorus poisoning on carbohydrate tolerance, *Jr. Biol. Chem.*, 1923, lviii, 515-522.
- ¹⁶STEWART, M. J., VINING, C. W., and BIBBY, J. P.: Subacute yellow atrophy of the liver in a case of syphilis following treatment with galyol, (*Proceedings of Path. Soc. of Great Britain and Ireland*), *Jr. Path. and Bact.*, 1919, xxiii, 120-122.
- ¹⁷*Physician's Bulletin*, Eli Lilly Co., 1929, lxviii, 17.

Migrating Pneumonia*†

Certain Mechanical Factors in Its Production, Prevention, and Treatment

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A CLOSE study of postoperative massive collapse of the lung (pulmonary atelectasis) indicates its marked similarity to pneumonia. These two conditions have many characteristics in common and, from the study of atelectasis, we may draw certain deductions relative to pneumonia.

As observed by Norris and Landis,¹ "practically every case of pneumonia spreads to some extent. In some cases it slowly extends spreading from lobe to lobe by contiguity; in others the process apparently develops afresh at different points in the same or the opposite lung", and, "in double pneumonia, both bases may be affected simultaneously or the apex of one lung and the lower lobe of the opposite lung may be involved". This migrating or wandering pneumonia, which moves from place to place within the same or the opposite lung, also has been

designated as "creeping", "progressive", and "extending" pneumonia.

We believe that migrating atelectasis and migrating pneumonia are attributable to the same factors. This conclusion is reached by studying the changes in the position of the abnormal signs after the patient has changed from one posture to another. Pneumonia, as well as atelectasis, migrates to definite areas, in accordance with the principles of "internal drainage",² i.e., the spilling of pus or secretion from place to place within the same or the opposite lung, plugging bronchi, obstructing air flow, and causing infection of previously uninvolved areas. The spilling is on a mechanical basis. It depends upon the amount and viscosity of the intrabronchial pus, the posture of the patient, the course of the bronchial stems, and the relative position of the various bronchial openings. (Figures 1, 2, and 3)

The changes within the bronchi are influenced further by the virulence of the organisms within the intrabronchial exudate; but there will be no spilling or migration in the absence of excess intrabronchial secretion.

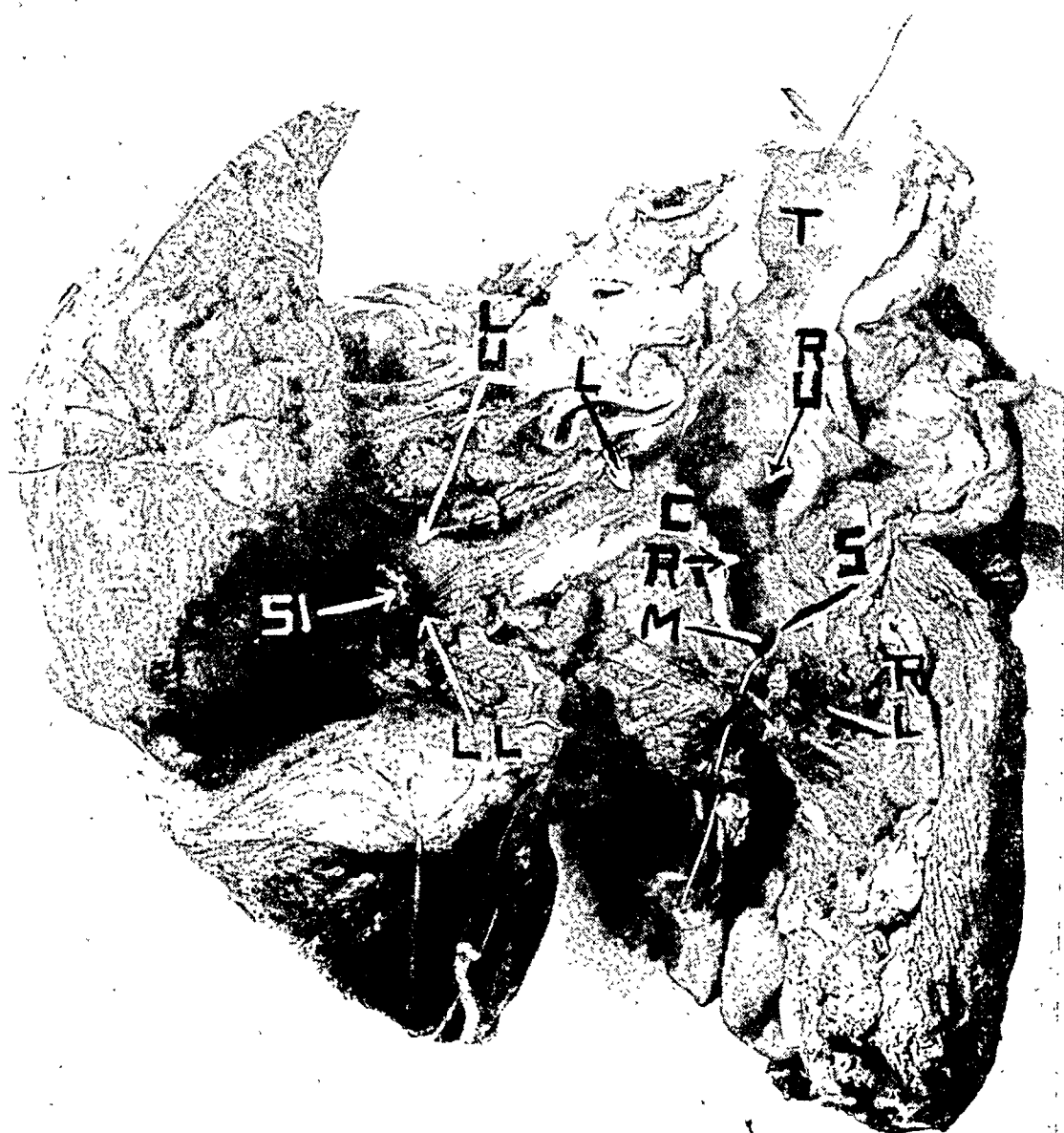
Bronchoscopic examinations support these deductions and show that thick

*Read before the American College of Physicians, San Francisco, California, April 8, 1932.

†From the Department of Surgery, University of California Medical School, San Francisco; Department of Medicine, French Hospital, San Francisco; and Department of Thoracic Surgery, St. Mary's Hospital, San Francisco.

pus gravitates less readily than thin watery material. Should thick sticky pus be dislodged from the original site of a pneumonic area, it is likely to plug a large bronchus, shut off air flow from a great portion of a lobe or an entire lung, and give signs of lobar pneumonia over a new site.

Thinner material spills with greater ease, runs deeply into the lung, and either plugs or fills one or several small minor bronchi to produce signs of bronchopneumonia. Such migrations of both bronchopneumonia and lobar pneumonia owe their origin to the same cause, namely, internal drain-



—Courtesy of Jr. Am. Med. Assoc.

FIG. 1. Specimen illustrating the anatomy of the tracheobronchial tree, the free communication between the various bronchi, and the ease with which the material may spill from one to the other. Note the position of the right upper lobe bronchial opening (RU) almost directly opposite the bifurcation of the trachea (C). L- Left main bronchus dividing into the left upper (LU) and left lower (LL). SI- septum between these two bronchi. R- right main bronchus divided by the septum (S) into the middle (M) and the lower lobe bronchus (RL).

age. Any apparent difference in the two is attributable to the varying viscosity of the intrabronchial secretion and the size of the plugged and infected bronchi. One can predict even

lobe. When the patient lies flat upon the affected side, there is little opportunity for spilling or migration to other lobes. (Figure 4) If he is flat upon his back instead of upon his side,

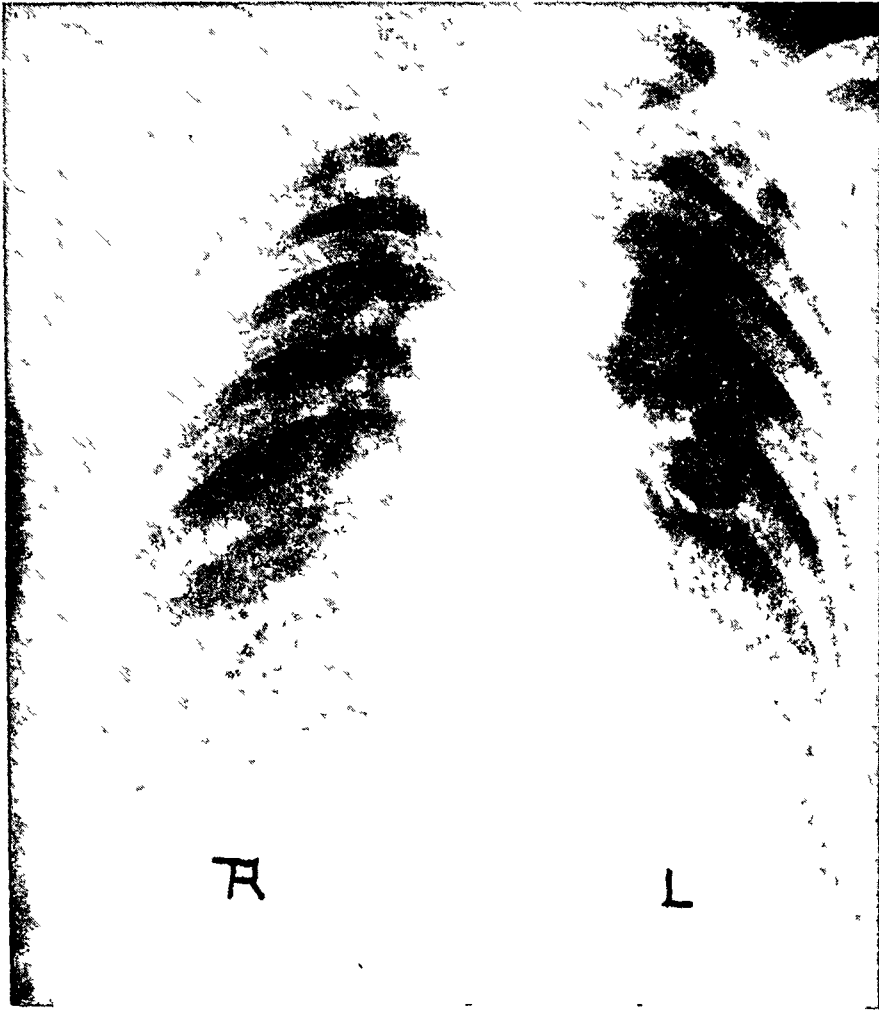


FIG 2 Iodized oil roentgenogram to illustrate the facility with which intrabronchial material can migrate by "internal drainage". The oil was introduced without the use of any type of anesthesia with the patient leaning slightly towards the left. Note the absence of oil in the right lung. Compare with plate 3.

the sites to which pneumonia will migrate for these are determined by the posture of the patient.

For example, let us consider the probable sites of migration of a pneumonia beginning in the right upper

lobe. When the patient lies flat upon the affected side, there is little opportunity for spilling or migration to other lobes. (Figure 4) If he is flat upon his back instead of upon his side,

to the other. (Figures 5 and 6) Should the patient be placed in the semi-Fowler or sitting position, the spilling of pus from the upper lobe is facilitated. This material gravitates along the floor of the right main bronchus to the first available opening, small amount of secretion plugging the bronchus and the comparatively large area over which the abnormal physical findings are elicited. Every change in the position of the patient leaves him liable to the spilling of pus and the consequent migration of the pneumo-



FIG. 3. Same patient as in figure 2. The oil spilled from the left lung into the right when the patient lay upon the right side. There was no cough associated with this spilling. It was caused by the change in the posture of the patient.

which is the posterior minor bronchus of the lower lobe. By plugging or filling this small bronchus, it produces abnormal findings at the area below the angle of the right scapula.

All clinicians are familiar with the frequency of pneumonia at this site, but attention should be called to the striking disproportion between the

nia. The progression of the disease into the sound lung when a position on the unaffected side is assumed, should be sufficient evidence of the influence of posture upon migration. The high position of the right upper lobe bronchus almost directly opposite the bifurcation accounts for the spread of pneumonia from the right upper to the

left lower lobe and vice versa. (Figure 7)

We have observed very closely the changes in the physical findings following alterations in the posture of

quently there is hyperresonance over the area to which the pus has spilled but the breath sounds are markedly reduced or completely absent. This is exactly what one finds in the case of



FIG. 4. Iodized oil injection of the right lung demonstrating the horizontal course of the right upper lobe bronchus (RU) and the difficulty of pneumonia migrating from this area to new sites when the patient lies upon the affected side

patients who have pneumonia. Râles occasionally appear at new areas and there is an interference with the inflow and outflow of air at this particular region. Later there is a change in the percussion note. More fre-

an intrabronchial foreign body. The signs are caused by the obstruction of the bronchus and the trapping of air resulting in the production of an obstructive emphysema. The strongest argument in favor of the mechanical

production of this migration is that the signs change with a rapidity equal to those produced by an intrabronchial foreign body. Following the absorp-

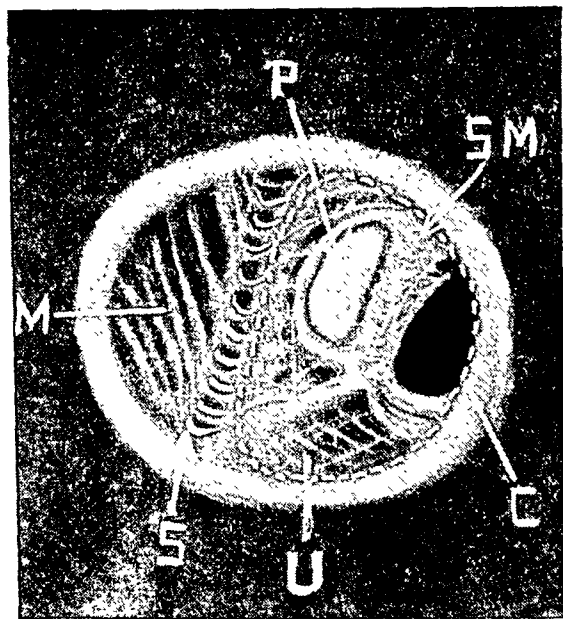


FIG. 5. Diagrammatic sketch of the bronchoscopic appearance of the right upper lobe bronchus. S-septum separating the upper lobe bronchus (U) from the main stem bronchus (M). Note the nearness of the minor divisions (P and C). This close proximity permits material to migrate from one to the other. SM-minor septum.

tion of the air which is trapped beyond the plug of pus, an atelectasis ensues, infection sets in, and if the condition is not corrected, a true pneumonia of the migratory type becomes established at this site.

The acceptance of this mechanical factor in the production of migrating pneumonia enables us to adopt measures not only to prevent but also to treat the condition. The patient can be kept in such a position as to lessen the likelihood of spilling to new areas. Nevertheless, even in these instances, there may be a welling up of pus to such an extent that there is some overflow to the dependent and accessible regions.

Prevention of migration really rests

upon the removal of the intrabronchial pus. This often can be attained through expectoration. It is facilitated by the administration of expectorants and a saturated solution of potassium iodide which lessens the viscosity of the secretion. Steam inhalations serve the same purpose, while inhalations of pure carbon dioxide gas so widen the bronchi that the evacuation of the intrabronchial material is possible.

With all these methods of removal, the posture of the patient should be such that the material will drain out of the lung rather than deeper into it. These postures are extremely variable and depend on the site of the pneumonia. Atropin, which tends to thicken secretions, is contraindicated for these patients because it interferes with expectoration.

Should it be noted that secretions are spilling and are not evacuated following cough and postural exercises, bronchoscopic removal of the secretion, and bronchoscopic treatment of the affected regions should be instituted before the onset of atelectasis and subsequent pneumonia. In trained hands, the bronchoscopy can be done in from one to two minutes under local anesthesia without particular discomfort to the patient.

These mechanical principles are offered as adjuncts in the management of patients with pneumonia without any intention of minimizing the value of the other general therapeutic measures of proven worth.

CONCLUSIONS

1. Postoperative massive collapse of the lung (pulmonary atelectasis) has many characteristics in common with bronchopneumonia and lobar

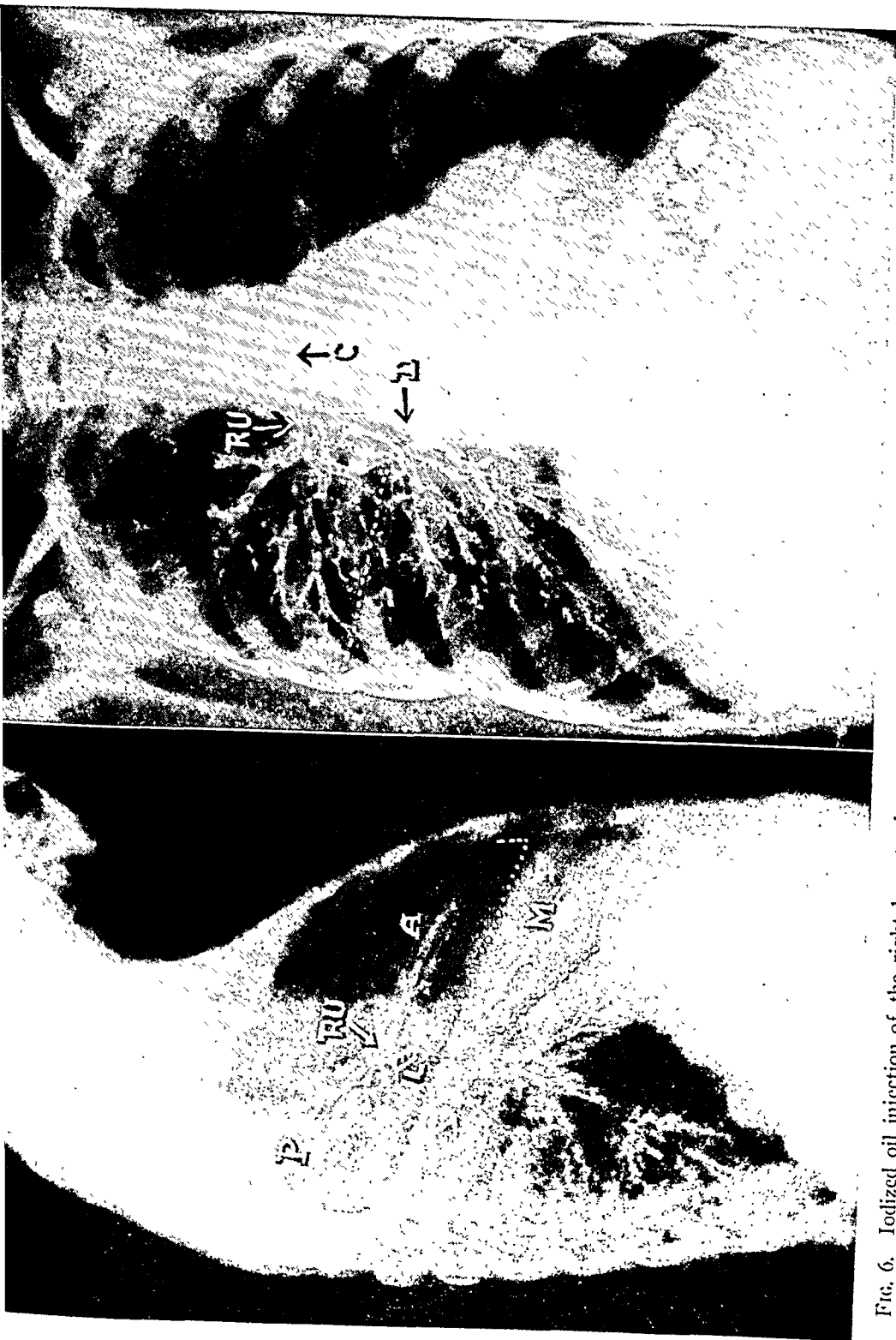


FIG. 6. Iodized oil injection of the right lung to demonstrate the close relationship of the branches of the upper lobe bronchi. RU- right upper lobe bronchus dividing into its anterior (A), posterior (P), and lateral branches (L). M- middle lobe; C- carina (bifurcation of the trachea); D- point of origin of the middle and lower lobes.

pneumonia. Both show strong tendencies to migrate to identical areas following similar changes in the posture of the patient.

2. Evidence is offered to show that

3. This whole problem is intimately connected with the mechanism of "internal drainage", i.e., the spilling of secretion from place to place within the same or the opposite lung.

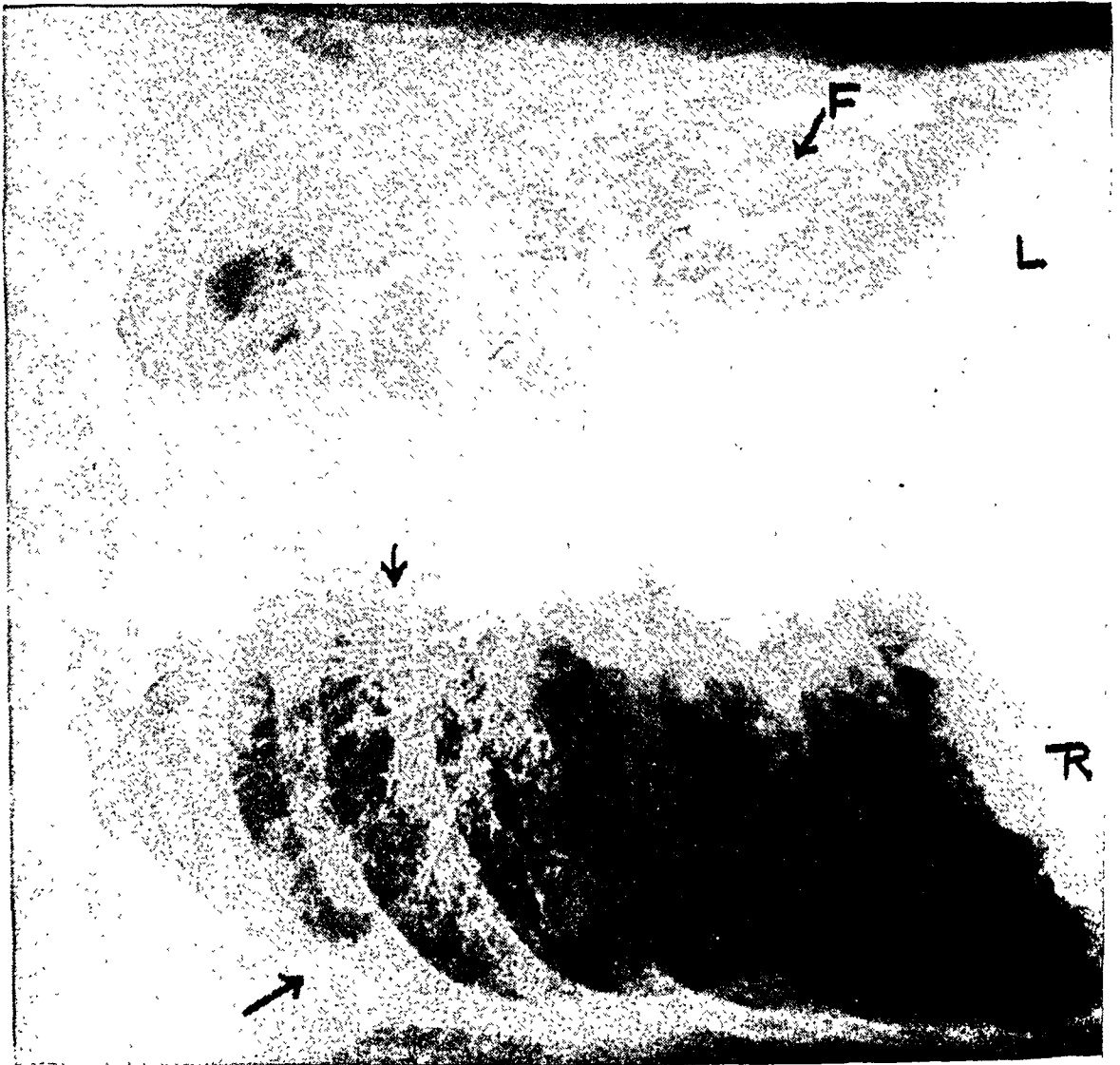


FIG. 7. Iodized oil introduced into a left lower lobe bronchial fistula (F) without the use of any type of anesthesia spilled across the bifurcation into the right upper lobe when the patient lay upon the right side. The facilities for the migration of secretion from the left lower to the right upper lobe are demonstrated also in figure 1.

the migrations in pneumonia are on a mechanical basis. They are dependent on the original site of the pneumonia, the posture of the patient, the intra-bronchial anatomy, and the amount and viscosity of the intrabronchial pus.

4. Thin secretion spills deeply into the lung, plugs small scattered bronchi and produces a migratory bronchopneumonia. More viscid material gravitates less readily. It leads to obstruction and infection of the major

bronchi resulting in a migratory lobar pneumonia.

5. The administration of expectorants, the use of saturated solution of potassium iodide to lessen the viscosity of the secretions, and the adoption of proper postures offer a means of evacuating the bronchi and preventing the

internal drainage which is responsible for the production of migrating pneumonia.

6. The bronchoscopic removal of the intrabronchial exudate is to be recommended whenever the patient fails to respond promptly to the other therapeutic measures.

BIBLIOGRAPHY

¹NORRIS, G. W., and LANDIS, H. R. N.: Diseases of the chest and the principles of physical diagnosis, 3 Ed., 1924, W. B. Saunders Co., Philadelphia, p. 464.

²FAULKNER, W. B., JR.: Internal drainage; its application in pulmonary suppuration, Jr. Am. Med. Assoc., 1930, xcv, 1325-1328.

Maintenance Dosage of Liver Extract in the Treatment of Pernicious Anemia*†

By PAUL J. FOUTS, M.D., and L. G. ZERFAS, M.D., *Indianapolis, Indiana*

IN presenting data relative to the maintenance dosage of liver extract or other substances potent in the treatment of pernicious anemia, it is necessary to define and state the requirements which this term implies. Beebe and Lewis¹ have clearly defined these requirements in a recent report of a large series of cases observed at the Thorndike Memorial Laboratory and at the Boston City Hospital. They stated that, "although the level of the red blood cells and hemoglobin serves as one important guide to the amount of therapeutic material necessary for the maintenance of health, there are other aspects of each case that should be recognized as important criteria in determining the amount of liver or potent substitute that should be taken. These other matters pertain to the patient's habits, symptoms and physical signs, the presence or absence of complications, and the detailed histology of the blood itself."

There is much information relative to the course of this disease before the advent of liver, kidney, and stomach therapy with which to compare the re-

sults obtained following the administration of effective therapeutic substances over prolonged periods of time. It is essential that "prolonged periods of time" be emphasized, because of the occurrence of spontaneous remissions, the duration of which is known to vary considerably in the same and in different patients.

It has been a common experience to see patients attempt to regulate their own dosage. Many times both patient and physician are misled as to the determination of the proper maintenance dosage, because prolonged periods are often required to determine the effects of an increased or decreased daily amount of potent substance. The psychology of these patients under treatment and the insidious nature of the disease are other factors that constitute serious obstacles in their proper treatment. It is obvious that frequent observations relative to the clinical aspects of the disease and to the state of the blood are imperative at frequent intervals for the proper management of the patient.

We have selected, from a series of 150 cases treated, fifty-nine patients with typical pernicious anemia, on the basis of the duration of treatment (none less than one year), frequency of observations, and consistency with

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†From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, and the Department of Medicine, Indiana University School of Medicine.

which they ingested the prescribed amount of liver extract. The average duration of treatment of these patients was thirty-six months, ranging from twelve months (two cases) to fifty-seven months. At the beginning of treatment, fifty-seven of the fifty-nine patients were admitted to the hospital in severe relapse, and afterwards were released to the "Out-Patient Department", where they have continued treatment under our personal observation and management. The two remaining patients were admitted to the "Out-Patient Department" while in a remission. As a rule these patients were regular in attendance, reporting at monthly intervals, at which time they were supplied gratis with a sufficient amount of Liver Extract No. 343* to last until their next visit. Under these circumstances, the regularity of their visits was quite imperative. Occasionally certain patients attempted to make the monthly quota of extract do for two months or longer and others omitted therapy altogether until it became obvious to them that they needed further treatment.

The average red blood cell counts, percentages of hemoglobin, and daily amounts of extract which they consumed were computed in each case studied, beginning with the time that the red blood cell count and hemoglobin reached normal levels. It is regrettable that each individual case cannot be presented in full detail as to the blood determinations and clinical findings, as there are many points of interest which are not recorded or

which are obscured by the general averages. The daily amount of potent extract to maintain the blood at normal and to keep the health of the patient in a satisfactory state was calculated over a period of not less than one year. In the majority of instances, either smaller daily amounts had been taken previously for a year or more and found insufficient, or larger daily amounts were reduced for a similar period of time without appreciable changes in the blood or in the health of the patients. The average maintenance dose of potent liver extract, so computed, represents the minimum daily amount as determined in this series of patients during an average period of thirty-six months. We have used the same lower limits of normal as those stated by Beebe and Lewis—4,500,000 red blood cells per cubic millimeter and 85 per cent hemoglobin. The hemoglobin was determined by the Newcomer method. There were a few cases in which the average percentage of hemoglobin was slightly less than 85 per cent which were included in the normal group, since the red blood cell counts and the general health of the patients were satisfactory.

An analysis of the series of fifty-nine patients treated showed that thirty-eight (64.4 per cent) maintained normal red blood cell counts and hemoglobin percentages while taking the daily amount of extract derived from three hundred grams of liver, or less. These patients were classified as Group I. The twenty-one remaining cases (35.6 per cent) did not maintain normal red blood cell counts and hemoglobin percentages while taking the

*The liver extract was supplied by Eli Lilly and Company.

daily amount of extract derived from three hundred grams of liver and were classified as Group II.

In table 1 the patients composing Groups I and II have been further subgrouped as to the average daily amount of extract taken. The average

tract derived from 400 and 600 grams of liver. These patients had previously been given the amount of extract derived from 300 grams of liver, but their blood and hemoglobin either did not reach normal or was not maintained at normal for any length of time

TABLE I

The data in table 1 show the number of patients who did or did not maintain normal red blood cell counts and hemoglobin percentages while taking various daily amounts of potent liver extract. The amount of liver extract is expressed in terms of the number of grams of whole liver from which it was derived, as it is generally considered that 25 to 30 per cent of the active principle contained in liver is lost by fractionation.

	GROUP I				GROUP II		
	LESS THAN 100 GRAMS	100 GRAMS	200 GRAMS	300 GRAMS	400 GRAMS	600 GRAMS	300 GRAMS†
Number of cases	3	6	10	19	4	3	14
Average age in years	57	55.1	53.7	55.5	58.2	44.3	59.5
Average number of red blood cells per cubic millimeter (in millions)	5.32	4.85	5.01	4.84	4.92	4.83	3.92
Average hemoglobin percentage	89.2	82.5*	86.7	85.6	86.2	88.9	77.2
Average amount of liver extract (in grams)	60	100	200	300	400	600	328

*Three patients who had normal red blood cell counts, but whose hemoglobin percentages were below 85 per cent, were considered essentially normal, since their general health was in a satisfactory state.
†Two patients in this group received the daily amount of liver extract derived from six hundred grams of liver.

red blood cell count, percentage of hemoglobin, and the average age of the patients in each subgroup have been determined. It can readily be seen from an examination of this table that there is a great variation in the daily amount of extract ingested capable of maintaining the blood and hemoglobin at normal levels over a period of time greater than that usually observed in spontaneous remissions. Seven of the patients in Group II reached and maintained normal red blood cell counts and hemoglobin levels while taking the daily amount of ex-

on this dosage. The remaining fourteen patients in Group II ingested inadequate daily amounts of the extract when they took regularly the amount derived from 300 grams of liver. Seven of the fourteen patients still living are receiving large daily amounts of the extract, but sufficient time has not elapsed to evaluate the dosage for inclusion in this paper. Since thirty-eight of the patients (64.4 per cent) maintained normal blood counts and hemoglobin percentages on the daily amount of extract derived from 300 grams of liver and less, it is still neces-

sary to question why twenty-one (35.6 per cent) were unable to reach or maintain normal blood levels while taking regularly the daily amount of extract derived from 300 grams of liver.

extract derived from 223 grams of liver. This average daily amount we consider to be the minimum. The twenty-one patients in Group II maintained an average red blood cell count of 4.19 million and percentage of hem-

TABLE II

The data presented in this table correlate the blood and the clinical aspects of the fifty-nine patients treated with liver extract for an average period of thirty-six months, as separated into Groups I and II.

	GROUP I	GROUP II
Number of patients	38	21
Average age in years, on admission	55.1	58.1
Average red blood cell count in millions per cubic millimeter	4.92	4.19
Average hemoglobin percentage	85.6	80.9
Average daily amount liver extract (in grams liver)	223	381
Percentage of patients with moderate to advanced arteriosclerosis	47.2	71.4
Percentage of patients with chronic infections	2.6	28.6
Percentage of patients with noninfectious complications	18.4	52.4
Percentage of patients who had moderate to advanced central nervous system involvement at the onset of treatment	34.2	66.6
Number of patients who developed central nervous system involvement while on liver extract treatment	3	2
Number of patients who developed central nervous system involvement and later improved	1	0
Number of patients with moderate to advanced central nervous system involvement who improved during treatment	4	1
Number of patients with moderate to advanced central nervous system involvement who had an increase in this involvement during treatment	1	10
Number of patients who died during treatment	0	7

In table 2, the average red blood cell count, hemoglobin percentage, and the daily amount of liver extract ingested have been correlated with the clinical aspects of the patients as previously classified (Groups I and II). The thirty-eight patients in Group I maintained an average red blood cell count of 4.92 million and percentage of hemoglobin of 85.6 per cent, while taking an average daily amount of

oglobin of 80.9, while taking daily the average amount of extract derived from 381 grams of liver. While this average daily amount was much greater than that recorded for Group I, it is still far below the minimum for this group and, therefore, inadequate. The average age of the patients in Group II was only slightly greater than that of Group I. In comparing the clinical aspects of these two groups, it is inter-

esting to note that, despite the slight difference in the average ages, the patients of Group II showed a much higher incidence of arteriosclerosis. The usual clinical means for determining arteriosclerosis were employed, such as digital palpation of the peripheral arteries, ophthalmoscopic examination of the retinal vessels, and blood pressure determinations.

The percentage of complications of an infectious and a noninfectious nature, separate and apart from the central nervous system involvement, was much greater in Group II than in Group I. These facts are significant, as the noninfectious complications include those degenerative conditions commonly seen in cases with advanced arteriosclerosis. In many instances the infectious processes involved the urinary tract, and some of these complications were secondary to the bladder disturbances resultant from advanced central nervous system involvement.

The incidence of central nervous system involvement on admission to the hospital was 34.2 per cent for Group I and nearly twice this percentage (66.6 per cent) for Group II. Therefore, it cannot be said that the greater incidence of central nervous system involvement in Group II occurred because of an insufficient amount of liver extract ingested while under treatment or because of a failure of the blood to reach or maintain a normal level. It can be said, however, that the number of patients whose central nervous system involvement advanced while under treatment was much greater in Group II (ten patients) than in Group I (one patient). Three patients in Group I and

two patients in Group II developed central nervous system involvement for the first time while under treatment, and only one of these patients improved (in Group I) while under treatment.

Four of the total number of patients in Group I, who had central nervous system involvement present at the onset of treatment, improved during liver therapy, in contrast to one patient in Group II. Many patients showed improvement of the minor signs and symptoms of central nervous system involvement while taking potent fractions of liver, but in this series we have considered only those cases showing moderate to advanced lesions, as interpreted by the clinical findings. Repeated clinical observations indicate that there are quiescent and actively progressive phases of the central nervous system involvement which may be recognized from time to time. During one of these active phases it is common to see the level of the red blood cells decrease; usually the decrease in the percentage of hemoglobin is much less, proportionately. Often large amounts of liver extract ingested daily (that derived from 1000 to 1200 grams of liver) will not be sufficient to cause the blood to return to normal or to prevent the progress of the central nervous system involvement at that time. During the entire period of observation, seven of the fifty-nine patients died while under treatment. These deaths occurred in Group II, while there were no deaths in Group I. All of the seven patients who died had advanced central nervous system involvement.

The data in table 2 indicate that

those patients with a higher incidence of complications, arteriosclerosis, and moderate to advanced central nervous system involvement (Group II) required, on the average, a greater daily amount of the active principle in liver to keep the blood and color index near normal. These findings are in accord with those reported by Beebe and Lewis.

An examination of the individual patients shows that an acute exacerbation of any or all of the above complications may lead to a severe relapse, even though the blood has been maintained at normal levels for a prolonged period of time while they are taking a given daily amount of liver extract. Occasionally, and for no apparent reason, relapses develop while they are taking the daily amount of potent extract which has maintained the blood and the state of their health at normal for as long as four and one-half years. Fourteen of the fifty-nine patients developed relapses some time during the period of observation, because of the omission of therapy or because of a reduction in the daily amount of liver extract. The time required to develop a relapse under either circumstance varied from two to eighteen months. In three cases more than one relapse occurred because of the omission of therapy. The length of time required to develop a relapse in the same patient varied from two to twelve months. Often a decrease in the hemoglobin percentage preceded, by several months, a reduction in the number of red blood cells previous to a relapse. However, a decrease in the number of red blood cells does not always follow, as the percentage of hemoglobin has

been observed to return to normal while the patient was taking the same amount of potent extract. It would seem advisable, under such circumstances, to administer large doses of iron, as recommended by Minot and his associates.

It is reasonable to believe that a relapse is conducive either to the development of or to the exacerbation of already existing complications seen in this disease, thereby establishing a vicious cycle. Therefore, it is imperative that the blood and the clinical condition of the patient be observed closely at frequent intervals. In the presence of or at the onset of such a cycle, the daily amount of liver extract should be increased sufficiently to, at least, maintain the blood of the individual patient at a normal level. If for any reason the daily administration of large amounts of liver extract by mouth is not feasible during this time, the parenteral use of liver extract is indicated.

CONCLUSIONS

1. Fifty-nine patients with pernicious anemia were treated with Liver Extract No. 343 by mouth for an average period of thirty-six months.
2. In Group I, thirty-eight patients (64.4 per cent) maintained normal red blood cell levels and percentages of hemoglobin, while taking the daily amount of extract derived from 300 grams of liver or less (average 223 grams).
3. In Group II twenty-one patients (35.6 per cent) did not maintain an average normal red blood cell count or hemoglobin percentage, while taking the daily amount of potent extract derived from 381 grams of liver.

4. The maintenance dosage of liver extract varied in different patients and in the same patient at different times.

5. The incidence of infectious and noninfectious complications, arteriosclerosis, and moderate to advanced central nervous system involvement was greater in Group II than in Group I.

6. The number of cases which showed an increase of the central nervous system involvement while under treatment was greater in Group II than in Group I.

7. Seven patients with advanced

central nervous system involvement in Group II died while on treatment, and no patients in Group I died.

8. In the presence of complications, both the blood and the clinical aspects of the patient should be observed closely, and, under any circumstances, amounts of potent material sufficient to maintain the blood at a normal level should be administered.

BIBLIOGRAPHY

- ¹BEEBE, R. T., and LEWIS, G. E.: The maintenance dose of potent material in pernicious anemia, *Am. Jr. Med. Sci.*, 1931, clxxx, 796-812.

Cardiospasm with Associated Arthritis*

By JOHN H. FITZGIBBON, M.D., F.A.C.P., Portland, Oregon

MANY etiological and contributing factors have been mentioned in the literature of arthritis, but cases in which the condition is associated with esophageal obstruction must be relatively rare.

For five years, I have had under observation and treatment a patient in whom cardiospasm and arthritis are intimately associated. As symptoms of arthritis have at times accompanied the appearance of difficulty in swallowing and have improved after dilatation of the stenosis, it seems worthwhile to report the case as one in which there appears to be an intimate etiological relationship between esophageal obstruction and arthritis.

CASE REPORT

Mrs. L. S. B., age thirty-one, was first seen May 4, 1927, in consultation with Dr. Frank McCauley and Dr. Wilson Johnston. She gave a history of cardiospasm of twenty years' duration. The stricture had not been dilated since 1919. As the result of marked obstruction and difficulty in swallowing, she had lost a great deal of weight. Her chief complaint, however, was generalized arthritis, on account of which she was confined to bed.

In June 1926, she had been very ill with pneumonia, and had been in bed for several weeks. Painful swelling of the feet and ankles appeared at that time. Following a diagnosis of pulmonary tuberculosis, she went to Arizona, where her chest condition

improved and the lesion was pronounced arrested. Arthritis of the finger joints and wrists developed in October and November 1926. Four infected teeth were extracted at that time. In January and February 1927, swelling and pain in the joints increased and she returned to Oregon in March with her shoulders, knees, hips, wrists, ankles, and finger joints involved. She was unable to walk and was confined to bed.

Her tonsils had been removed in 1919, but a small amount of tonsillar tissue remained and was removed by Dr. Johnston, May 5, 1927.

Difficulty in swallowing had gradually increased over a long period of time and she was extremely weak. A large amount of mucopurulent, blood-streaked material mixed with food was frequently regurgitated.

Physical examination was negative except for generalized arthritis with swelling.

Laboratory findings were as follows: Urinalysis, negative. Hemoglobin, 89 per cent. Red blood cells, 4,704,000. White cells, 8,700. Polymorphonuclears, 64 per cent. Small lymphocytes, 24 per cent. Large lymphocytes, 2 per cent. Coagulation time, 7 minutes. Blood Wassermann, negative.

X-ray examination of the esophagus showed a markedly dilated esophagus with obstruction at the cardia. (Figure 1)

It was hoped that her general condition could be improved by relieving the esophageal obstruction. Several attempts were made, using the Sippy air bag dilator introduced over a piano wire guided by a previously swallowed silk thread. It was possible to introduce the bag into the stricture, but inflation was not followed by improvement, for the bag tended to slip out of position. Fluoroscopic examination while the bag was being inflated showed that as the

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bag filled with air from the upper end it slipped upward into the esophagus and out of the stricture. As the esophagus was greatly dilated, there was room for the flexible shaft of the instrument to bend lat-

brought to the office for treatment and did not wish to make the trips often because of the inconvenience and the pain in the joints. It was necessary to carry her to and from the automobile. During this period she re-

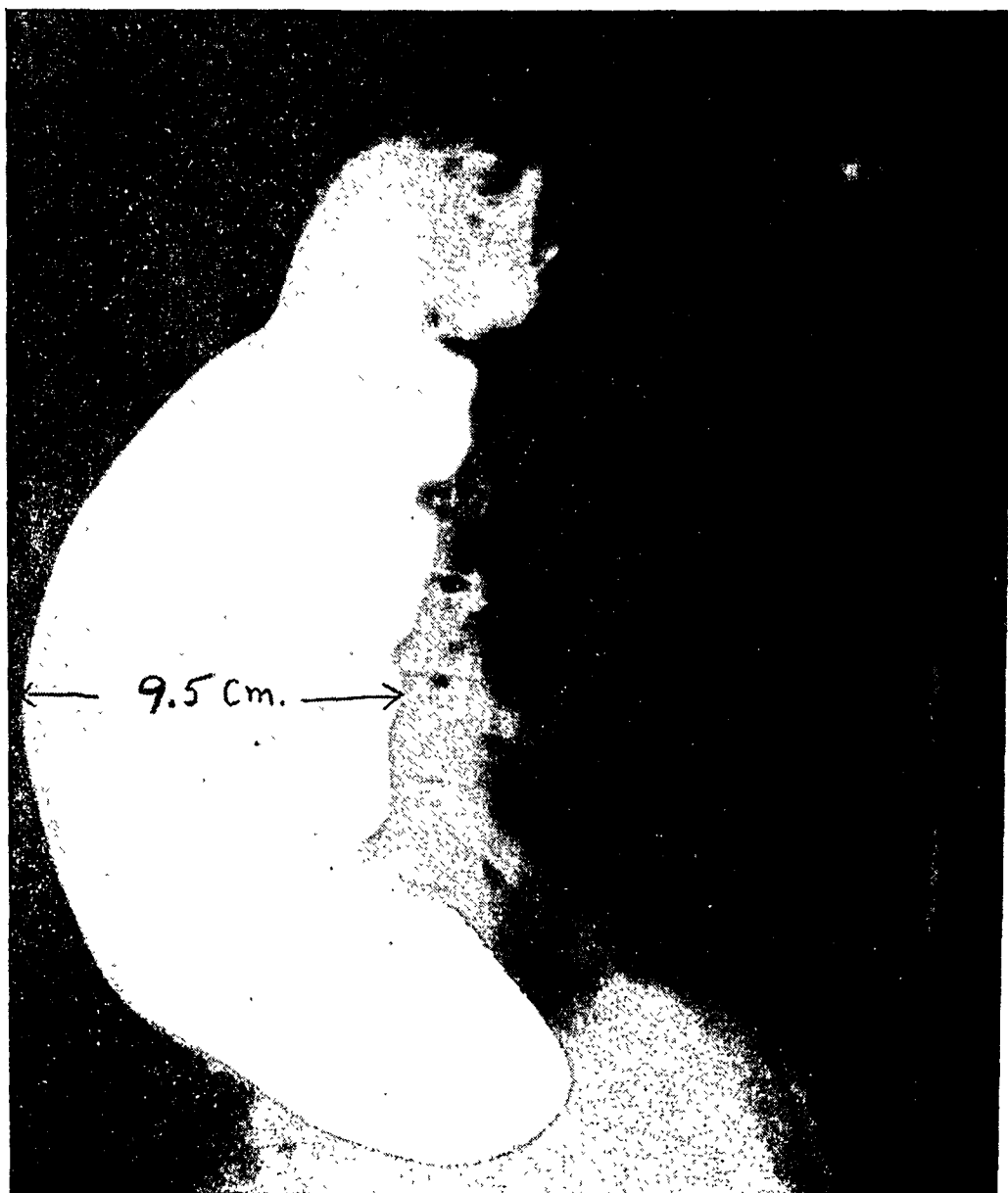


FIG. 1. Dilated esophagus due to cardiospasm.

erally and permit the bag to slip upward. The instrument was then modified¹ so that air entered from both ends simultaneously, and no difficulty was experienced in successfully dilating the stricture.

The failures with the original dilator consumed a great deal of time. She was

ceived quartz light and diathermy treatments from Dr. W. D. Lockwood. The esophagus was lavaged each evening, in the hope of relieving the local inflammation due to retention of food and secretions.

After successful dilation with the modified dilator, July 6 and 15, 1927, there was very

little difficulty in swallowing, and improvement in the arthritic symptoms began. Improvement continued and in September she was able to walk without pain. Her weight and general condition improved at the same time. She has experienced very little difficulty since. She has reported for treatment off and on, especially when difficulty in swallowing develops.

In January 1931, swelling and pain in the joints of the right hand and foot, reappeared, associated with difficulty in swallowing. Following satisfactory dilation of the cardia, these symptoms cleared up.

On November 3, 1931, she reported that she was four months' pregnant. As there was some difficulty in swallowing, and it was feared that this might increase during the remaining months of her pregnancy, her physician was consulted and the cardia was dilated with moderate pressure. On March 25, 1932, she returned, having passed through a normal pregnancy and delivery, but complained of a return of her difficulty in swallowing, associated with pain in the metacarpo-phalangeal joints of the right hand and the ankle and wrist joints. There was also a ganglion of the extensor tendon sheath of the index finger of the right hand.

The esophagus was dilated on April 26,

1932 and her joint symptoms have responded as usual.

COMMENT

From the course of this patient's arthritis, it seems reasonable to assume that improvement was the result of relieving the stricture of the esophagus. Previous to dilatation, she had regurgitated large amounts of mucopurulent, blood-streaked material from the esophagus and showed signs of having rather marked esophagitis due to retention above the stricture. Would it not be fair to draw the conclusion that the inflammatory lesions in the esophagus have acted as foci of infection which have activated the arthritis, and that drainage resulting from relief of the stenosis has permitted healing of these lesions with improvement in arthritic symptoms?

REFERENCE

- ¹FITZGIBBON, J. H.: Modifications of the Sippy cardiospasm dilator, *Northwest Med.*, 1930, xxix, 4, 171.

A Study of 800 Abnormal Electrocardiograms and Associated Clinical Conditions*

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THE purpose of this communication is to emphasize the practical value of the electrocardiogram for the study of cardiovascular diseases. The tracing is based on the electrical reactions of the heart muscle during each complete cycle of action and rest. The evolution of our knowledge of the cardiogram dates back to Matteuci, who in 1843 reported the existence of reactions or currents originating in the heart muscle. The studies of Engelman, Marey, Burdon, Sanderson and Page, Gaskell, Kölliker and Mueller, and Waller, led up to the development of the string galvanometer by Einthoven in 1903. Since then there has been a rapid increase in the use of string galvanometers for research and clinical studies of the various abnormal cardiac mechanisms. The work of Wenckebach, McKenzie, Lewis, and Nicolai in Europe, and Cohn, Herrick, Smith, Wilson, Pardee, and White in this country must be mentioned as taking a leading part in the development of our present knowledge of electrocardiography.

Today the internist must realize that cardiovascular disease forms perhaps

the most important group in his field to be studied and mastered. From the standpoint of morbidity and mortality it heads the list, and our program at this clinical session emphasizes this fact by devoting eighty-five periods to various phases of this group of diseases. In many diseases, such as small-pox, typhoid fever, diphtheria, scarlet fever, and tuberculosis, prophylaxis and therapeutic management have been well standardized, and as a result the physician and the laity are in a position to coöperate in the care and control of these diseases. In circulatory diseases, either acute or chronic, these phases are not so generally understood.

In the study of 800 abnormal cardiograms, we find all groups of cardiac diseases represented. They may be classified into three main groups: (1) those that are supposedly due to irritation of the myocardium; (2) the infections; (3) the degenerative processes.

IRRITATION OF THE MYOCARDIUM

In the first group we include the arrhythmias, represented by premature beats, paroxysmal tachycardia and simple tachycardia. The etiology may be toxic, directly affecting the myocardium, as occasionally seen in excessive use of tobacco, tea or coffee; or it

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may be temporarily produced by some acute infection. We must also include in this group the irritations of neurogenic origin, which occur from reflex gastro-intestinal disturbances, fear and fatigue. In this series there were thirty-seven cases with premature beats and six with paroxysmal tachycardia in which no specific evidence of cardiac disease could be discovered from history or physical findings. Focal infections were considered as possible causes but chronic follicular tonsillitis, sinusitis, dental abscesses, or acute infections, such as influenza, were not strikingly in evidence in this group of cases, and removal of some of these sources of infection was disappointing in its results. Modification of habits with reference to tea, coffee, tobacco, and elimination of intestinal disturbance and fear of serious cardiac disease, were much more productive of improvement. Premature beats were found in a considerable number of the cases belonging in the degenerative groups, but were not the main factors interfering with the well being of the patient, and apparently had little prognostic significance.

THE INFECTIONS

The second group includes those having valvular lesions and associated myocarditis, usually the result of acute endocarditis with extension into the myocardium, and occasionally involving the pericardium. The great majority of these cardiac insults occurred in early life. Eighty-two cases belonged in this group, fifty males and thirty-two females, and 57 per cent of them were less than fifty years of age.

The prevailing infections noted in the history were inflammatory rheumatism, chorea, acute and chronic tonsillitis, and influenza. The percentage of cases having had measles, diphtheria, scarlet fever, pneumonia and typhoid fever was not above the average found in the whole group and these diseases could not be considered of special etiological significance except in an occasional case. The lesions found were: mitral stenosis, 60; mitral regurgitation, 11; aortic regurgitation, 9; and aortic stenosis, 6. In four cases more than one valve was involved, and in three cases of mitral regurgitation there was slight suggestion of mitral stenosis, and many of those with mitral stenosis as the predominating lesion were complicated by regurgitation. Experience convinces me that the percentage of cases with pure mitral regurgitation is very small. In the 800 cases studied, 164 had systolic apical murmurs that were considered functional. The electrocardiographic findings revealed 13 with premature beats, 38 with notched *P*-waves, and 10 with prolonged *P-R* intervals. Eleven had auricular fibrillation, in most cases in conjunction with mitral stenosis, and 11 had low voltage. Poor *T*-waves were as follows: 31₁, 38₂, 34₃, and inverted *T*'s, 12₁, 20₂, 27₃, all suggesting definite myocardial changes probably due to myocarditis. There were 16 cases that had arteriosclerosis in addition to the valve lesions, and we noted 16 with *Q*-waves larger than 25 per cent of the tallest *R*-wave. All of the 82 had abnormal cardiograms but those with the simpler or less extensive valve lesions revealed only minor

changes such as prolonged *P-R* intervals, notched *P*-waves, and *T*-waves of low voltage.

DEGENERATIVE PROCESSES

The third group, comprising degenerative types, includes cardiograms of auricular fibrillation, bundle-branch block, heart block and a variety of abnormal tracings such as inverted *T*-waves, those of low voltage, and large *Q*-waves, in various combinations. We found 101 with bundle-branch block, 7 with heart block, 55 with auricular fibrillation, and 512 with myocardial degeneration with or without arterial disease in various degrees or angina pectoris. There were 511 males and 164 females in this group, and 568, or 84 per cent of these patients, were more than fifty years of age. These figures indicate a marked preponderance of the degenerative diseases in the males and confirm their occurrence in the later decades of life. In considering other etiological factors in this group, acute infections in early life seem to be of little importance. A history of influenza was obtained in 269 cases. This type of infection may aggravate an already established cardiac condition. Similarly chronic focal infections may be factors in hastening the progress of myocardial, if not of vascular, disease. The eradication of such foci seems justified.

In this group of 675 cases, the influence of heredity was shown to be of great importance, since in 72 per cent a family history of some type of cardiovascular disease was found. Among these, 111 had a positive history in both branches of the family and it is interesting to note that in these cases

manifestations of cardiovascular troubles began as a rule earlier in life than where only one branch of the family was involved. These facts strongly suggest that arteriosclerosis with its degenerative processes is constitutional in nature. Obesity must also be considered as a serious factor in hastening degeneration, as it occurred in 64 per cent of these cases. The early control of this condition will be considered later in discussing management of this group.

SYMPTOMS OF CARDIAC INEFFICIENCY

The symptoms that lead to suspicion of cardiac inefficiency are rather few in the early stages of degenerative cardiovascular disease. Dyspnea is practically always the first, but is frequently overlooked by both patient and physician. The patient often considers moderate dyspnea normal or due to advancing years or over-weight. It is of the utmost importance to determine the amount of effort that produces this symptom. If it occurs during minor or ordinary activities, it should be regarded as very suggestive of cardiac inefficiency. Marked shortness of breath is not apt to be noticed by the patient unless he indulges in vigorous exercise at frequent intervals. In this group of cases dyspnea occurred in varying degrees in 558 cases, and in many was the only subjective sign of beginning cardiac inefficiency. The most difficult cases to judge from the point of history and symptoms were those of very sedentary habits, and here a few vigorous hops or climbing a flight of stairs were usually a convincing proof of a limited cardiac efficiency.

Palpitation or heart-consciousness is perhaps the next most frequent symptom experienced in this group. It is essential to obtain a clear idea of what the patient may mean by palpitation, as it may be a simple tachycardia not related to effort. Palpitation was noted 322 times. When these two subjective symptoms, dyspnea and palpitation, appear together with arterial hypertension and obesity, we should not fail to make a thorough study of cardiovascular efficiency.

Chest pain or precordial discomfort is another important symptom; it does not always mean angina pectoris but may mean aortitis or some other form of heart disease. This symptom occurred 296 times but was radiating in type in only 140 cases and not all of the latter justified the diagnosis of angina pectoris.

Our examination included search for such objective findings as basal pulmonary congestion, abnormal heart sounds, blood pressure, cardiac hypertrophy, and cardiographic findings. Basal congestion was noted 166 times and is worthy of careful study from day to day as evidence of the patient's progress in overcoming decompensation. High blood pressure findings are of extreme importance as they give a picture of cardiac labor with the patient at rest and must be recognized as a handicap to the heart muscle. The systolic pressure was found to be above 150 in 415 cases, and below in 260; the diastolic was above 90 in 366, and below in 309 cases, showing a decided preponderance of blood pressures above 150/90 mm. Hg. In this group a larger percentage of those with blood pressure less than 150/90

occurred in the cases having bundle-branch block, auricular fibrillation, and in a group classified as simple chronic myocardial degeneration. Among these are many with arteriosclerosis, diagnosed as such, not by blood pressure, but by the presence of tortuous or palpable arteries and increased density of the aorta or peripheral vessels determined by X-ray. It was found important to make X-ray examinations of the arteries in the lower extremities in diabetes in order to anticipate possible gangrene, and in other cases to verify the probability of intermittent claudication, as these conditions are often found with a blood pressure less than 150/90. As the diastolic pressure progresses above 100, the prognosis for cardiac efficiency and length of life becomes increasingly unfavorable. In the study of blood pressure, whether high or comparatively low, it is very necessary to consider pulse pressure, which is of important significance in cardiac efficiency.

Heart murmurs are of less significance in this group. Only 49 were found which could be considered organic with reasonable certainty, as compared to 180 murmurs which were thought to be functional. All of these latter were systolic in time and nearly all were located at the apex. These functional murmurs are often diagnostic pitfalls and sources of anxiety to physician and patient respectively. To determine the true significance of murmurs is important, but of equal if not greater importance in this group of cases is a careful study of the heart tones, whether muffled, distant, or distinct, or of good quality. The term "heart tones" is not limited to the valve

sounds alone but includes the muscle tone, the result of the ventricular contractions. Tones that were poor in quality, or muffled, occurred in 324 cases in both the reclining and upright positions and aroused suspicion as to the quality of the heart muscle or the possibility of pericardial effusion. Gallop rhythm, which was found in 34 patients, occurred only in the more serious cases, and should always be regarded as an unfavorable prognostic sign.

In this group of cases of degenerative cardiovascular disease the cardiogram is of great value in forming an opinion of the condition of the myocardium. We found extra systoles 69 times, notched *P*-waves 16 times, prolonged *P-R* interval 44 times, all of which are of interest but not of great significance. Other findings deserve a little more detailed consideration.

Auricular fibrillation occurred 67 times and in this group must be considered indicative of myocardial degeneration. It often has a fair prognosis under proper therapeutic management. Bundle-branch block occurred 101 times and whenever found should be considered as positive evidence of extensive myocardial degeneration. In this series, where it was possible to follow up our cases, 55 per cent died within fifteen months after the bundle-branch block was discovered. Among these cases of bundle-branch block a few are found which present no symptoms either subjective or objective except the cardiogram, and these may go on for years without any symptoms of cardiac inefficiency; but in spite of this each case deserves careful management and the patient should be

warned against unusual effort. Muffled heart sounds are very frequently found to be accompanied by dyspnea, precordial discomfort, poor tolerance for exercise, moderately high blood pressure or evidence of a limited cardiac efficiency, and these cases should be managed with extreme care. The cases showing low voltage numbered 134, and in some of them repeated observations are deserving of special interest. A number of such cases has gradually developed impairment of cardiac efficiency and as a group they deserve a careful study with repeated observations to determine the prognostic value of this type of tracing.

THE SIGNIFICANCE OF SOME ABNORMAL CARDIOGRAMS

The inverted *T*-wave deserves mention, being found with considerable frequency in the degenerative cases. It occurred 231 times in T_1 , 172 times in T_2 , and 186 times in T_3 . Inverted T_1 and T_2 alone or in combination are considered of pathological significance, but inverted T_3 alone is not looked upon as evidence of disease. I am not sure that inverted T_3 is without significance, especially if T_2 is of low voltage. I am inclined to believe that a low T_2 with inverted T_3 will often develop into an inverted T_2 and T_3 and thus may be of pathological significance. In 11 cases where cardiograms have been taken at intervals over a period of years, I have found this change to occur, coupled with evidences of progressive cardiac inefficiency.

The *T*-waves of low voltage are of more frequent occurrence than the inverted *T*-waves, but in similar pro-

portions, there being 234 T_1 , 205 T_2 , and 207 T_3 of low voltage. Both the inverted T -waves and those of low voltage occur with greatest frequency in patients with general arteriosclerosis and obesity, and must be looked upon as positive evidence of myocardial degeneration. We find that not a few of the poor T -waves later become inverted. I have noted these changes in 15 cases. These observations are dwelt on in detail to emphasize the importance of low voltage T -waves as evidence of insidious changes taking place in the myocardium. They deserve our careful consideration when interpreting the cardiogram, and attention should be called to T -waves as being suggestive of low voltage before they reach the point of measuring 1 mm. or less.

Large Q -waves in Lead III of more than 25 per cent the height of the R -waves have been brought to our attention by Pardee as evidence of pathological lesions of the left ventricle. In our series, large Q -waves were found 257 times and occurred with greatest frequency in cases of angina and general arteriosclerosis. In 137 cases of angina, a large Q -wave was found 95 times. Here again I suggest the presence of an inverted T_3 and large Q -wave as still more positive evidence of myocardial disease as far as Lead III is concerned. Further study of the poor T and inverted T and large Q -waves should be encouraged and, where possible, the nature of pathological lesions of the myocardium determined.

The coronary or cove wave in coronary thrombosis is another abnormal picture that is of diagnostic value con-

firmatory of the subjective or objective findings of this serious cardiac condition. In my experience, the cove, or abnormal S - T interval, appears within a few days after the insult, and in the cases that survive and finally develop a fair myocardial efficiency, the tracing returns to approximately normal as far as the S - T interval is concerned. The nearer the tracing approaches to normal, the better the prognosis. Cases under observation for from three to seven years have tracings with little or no evidence of the coronary wave. This wave was found 26 times and occurred in cases of coronary thrombosis or angina pectoris only. In one case attacks of paroxysmal tachycardia occurred during a stormy convalescence. Here, absolute rest, small doses of quinidine sulfate and digitalis and proper use of sedatives, proved most effective in eliminating the attacks.

COMMENT

The management of the various types of cases found in this review may be briefly outlined. The premature beats and paroxysmal tachycardia are of minor importance but sometimes are very annoying to the patient. The best program in my experience is to eliminate anxiety or fear and consider focal infections and toxins, such as coffee, tea and tobacco, as possible causes. It is also important to eliminate reflex disturbances of gastrointestinal origin. In addition we should consider the advisability of the use of quinidine sulfate and sometimes of a mild sedative for relief. Auricular fibrillation, another form of arrhythmia, deserves a good prognosis under proper management. Careful judgment

must be used in the exhibition of quinidine sulfate, as permanent relief of arrhythmia results in only a small percentage of cases. It should be avoided in severe cases of mitral stenosis for fear of unpleasant complications. Whenever there is a suggestion of decompensation, digitalis is the remedy of choice. For the cases with arteriosclerosis and hypertension, bundle-branch block, and associated myocardial degeneration, it is very important to recognize myocardial changes as early as possible and take into consideration the effect of arterial hypertension, the condition of the pulse pressure and the presence of obesity.

In developing a program for these cases it is of great value to outline a proper amount of exercise, as experience proves that it is of extreme importance to maintain the best possible muscle tone and endurance in these individuals. Each case must be considered individually when developing a program of exercise. A careful weight reduction for the obese is of great importance. With patients under close observation, a rather vigorous program of weight reduction by diet and physiotherapy (hydrotherapy, heliotherapy, and massage) may be ventured in the more robust types, if definite evidence of myocardial inefficiency is lacking. In such cases a loss of five

to eight pounds a week may be risked; but with cases not under close observation, a loss of one or two pounds a week is usually safer. The control of food intake and exercise is of greatest importance in these cases. It is surprising how little food is necessary to maintain the desired weight when it is once established. In cases of marked hypertension, particularly those with high diastolic pressure and marked renal inefficiency, the protein intake can be safely reduced to 50 or 60 grams a day, or lower, over a considerable period of time. The use of fruits and fruit juices should always be encouraged and should furnish a considerable portion of the carbohydrate.

Experience convinces me that the greatest reduction in blood pressure and improvement in cardiac efficiency is obtained by reduction in weight, exercise, and a careful regulation of the individual's daily program with reference to work and recreation. Nervous tension, anxiety and fear, should be combatted in all of these cases. Institutional management affording careful observation over considerable periods of time, with the various forms of physiotherapy, dietetic regime and personal contact with the patient, usually produces the best results.

REFERENCES

- PARDEE, H. E. B.: Significance of electrocardiogram with large Q in Lead III, *Arch. Int. Med.*, 1930, xlii, 470-481.
- MUSSER, J. H., and BARTON, J. C.: Familial tendency of coronary disease, *Am. Heart Jr.*, 1931, vii, 45-51.
- BARNES, A. R., and WHITTEN, M. B.: Study of T -wave negativity in predominant ventricular strain, *Am. Heart Jr.*, 1929, v, 14-67.
- WOLFERTII, C. C.: Diseases of the heart and blood vessels, *Prog. Med.*, 1931, iii, 109-173.
- SCOTT, R. W.: Clinical aspects of arteriosclerosis, *Am. Heart Jr.*, 1932, vii, 292-304.

The Value of the Posterior-Anterior Chest Lead in Cardiac Diagnosis*†

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FROM the very nature of the cardiac action current, it is evident that the number of leads which can be used to conduct the current from selected skin zones to the string galvanometer is legion. It was inevitable that in cases where the three conventional leads failed to furnish enough information about the condition of the heart muscle, some other one, taken in another plane, would be tried in the hope that it might supply the needed data. Thus Waller¹ (1887) placed his electrodes all over the body, and in all the natural orifices, searching for "significant" leads. Lewis² (1909), studying the action of the auricles in fibrillation, discovered that the workings of this chamber could be best investigated by a special additional lead from the front to the back of the chest. To date this has found very little clinical application. Recently, however, Wolferth and Wood³ (1932) have applied the chest lead (from front to back of chest) in the diagnosis of coronary occlusion. They report one case where the three conventional leads were practically normal, except on the fourth day, whereas for eight days after the original infarction the Anterior-Posterior chest lead showed striking deviation of the *S-T* interval; and another instance where the evidence for coronary occlusion was present in only two leads, the first and A-P chest leads, the *S-T* deviation being much more striking in the A-P chest lead than in the first lead. They examined 33 non-coronary cases as controls and found no deviation of the *S-T* interval in the A-P chest lead in these cases.

Using a slightly different technique (smaller electrodes and a Posterior-Anterior direction, to be detailed later), and taking the chest lead in conjunction with the usual three in a series of 75 cases, 20 of which were normals, 50 cardiac suspects, and 5 "coronaries", we likewise found the additional chest lead very useful in determining the presence and extent of coronary involvement. We report the following case as especially demonstrative of the fact that the chest lead may point to a diagnosis of coronary occlusion where neither the clinical picture nor the E.K.G. taken with the usual leads suggests it. Often the conventional leads begin to show at a later date those changes seen days and weeks before by the chest lead.

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†From the Beth Israel Hospital, N. Y., and the U.S.P.H. Service Hospital, Stapleton, S. I. By permission of the Surgeon General, U.S.P.H.S.

CASE REPORT

H.M., white male, age 53, admitted to the U.S.P.H.S. Hospital, Stapleton, S.I., December 1, 1931. The past history was negative, except for moderate occipital headache and nocturia for ten years. On November 27, 1931 the patient's left leg suddenly felt weak,

and by the 30th it was limp and helpless. He entered with this sole complaint of weakness of the left leg.

Physical Examination. A well-developed white male of 53, not acutely ill. Head, heart, lungs, and abdomen negative. The left foot showed flaccid paralysis. The blood and

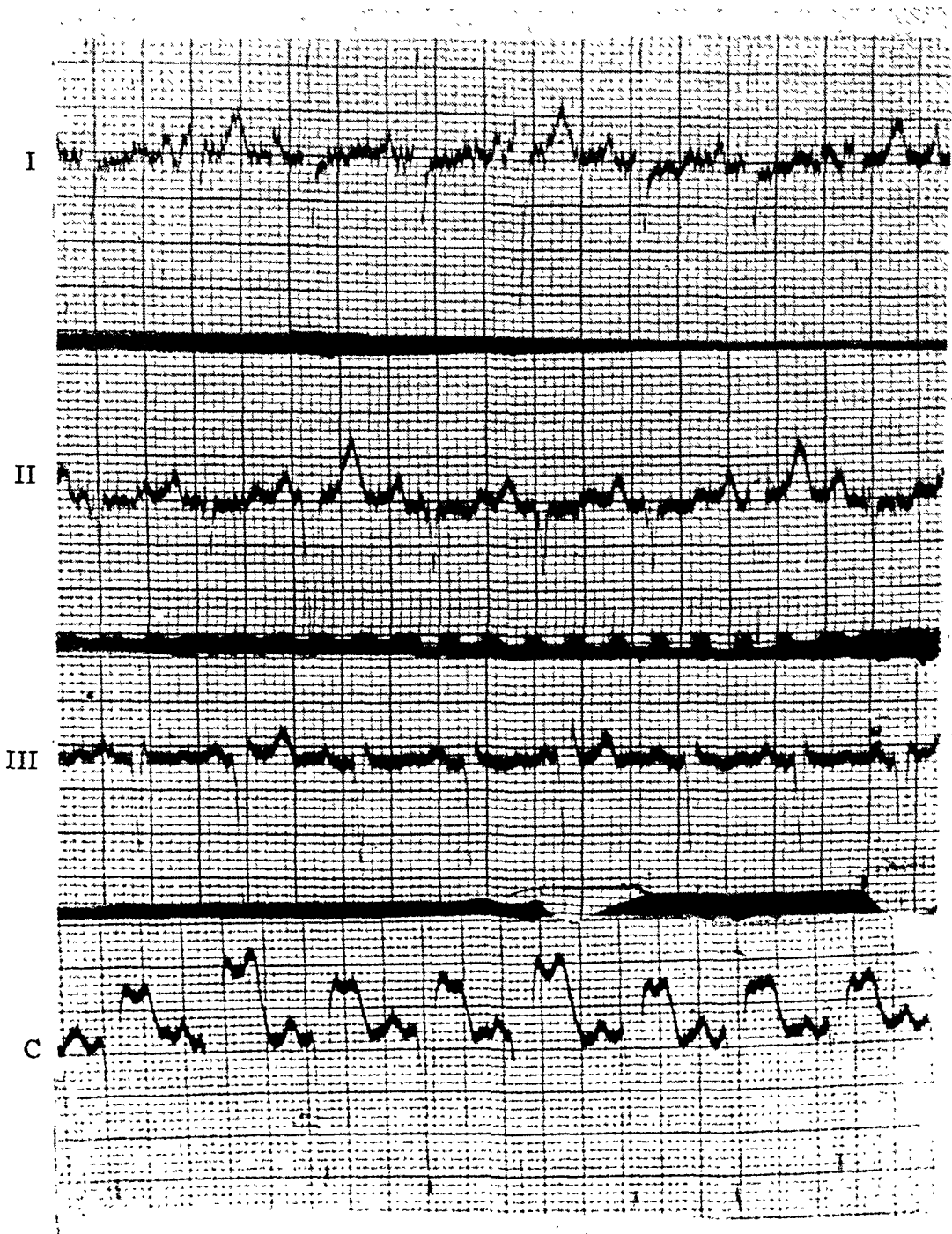


FIG. 1. (January 25, 1932). Patient showed no cardiac signs (except fall of blood pressure from 170 to 120 mm. Hg in three weeks). Leads I, II, and III are considered as take-off in Lead III. The Posterior-Anterior chest lead shows, however, an S-T elevation of fully 5 millimeters—practically pathognomonic of coronary occlusion.

spinal Wassermann, urine and blood count were all negative. Temperature 37°; pulse 90; respiration 20; blood pressure 170/90 mm. Hg. The headaches and hypertension suggested a cerebral thrombosis or hemorrhage as possible cause of this monoplegia. Aside from the hypertension the case appeared to be of neurological interest only. The patient did well under rest in bed and physiotherapy to the affected leg, complaining only occasionally of pain in the head or "an upset stomach". His blood pressure, however, fell from 170/90 mm. Hg to 120/66 mm. Hg, and it was thought advisable to make an electrocardiographic examination before transferring him to the Neurological Service. The graph obtained, January 25, 1932, using the three conventional leads and the Posterior-Anterior chest lead was surprising to the clinician (figure 1). The three usual leads showed every fourth beat to be ectopic; there was L.A.D. (old nomenclature). Aside from an occasional, questionable high take-off of the *T*-wave there was in these leads no definite indication of myocardial damage. In the P-A chest lead, however, instead of a symmetrical *T*-wave arising from the isoelectric point, there was fully 5 mm. elevation of the *S-T* interval, with total asymmetry of the *T*-wave. In spite of the negative evidence in the three conventional leads, and the absence of clinical symptoms, it was postulated that the patient had definite coronary damage, the type of curve suggesting an acute process.

The patient was transferred one day later (January 26, 1932) to the Neurological Service of the U.S.P.H.S. Hospital, Ellis Island, where his pulse was found to be very irregular and intermittent, varying between 62 and 104 during the next two days. This was thought to be due to the excitement incident to his transfer. A teleoroentgenogram taken at this time showed a contour of the heart suggesting slight enlargement to the left, but on the whole probably within normal limits in size and shape. There was slightly increased density in both bases and faint triangulation of the cardiac shadow suggestive of myocardial weakness. The E.K.G. of this date (January 26, 1932) employing only the three conventional leads

was reported as showing frequent ventricular extrasystoles, L.A.D., but no significant myocardial changes. After two days the patient began to feel better. The use of the left leg slowly returned in part, and he was discharged improved February 1, 1932.

Patient was readmitted to U.S.P.H.S. Hospital, Stapleton, S.I., on February 9, 1932 as an urgent case, complaining of pain in the upper abdomen and chest of four days' duration, beginning after a heavy meal, and accompanied by a mild non-productive cough and difficulty in breathing.

Physical Examination. Patient acutely ill; facies anxious, shallow and rapid breathing, moderately coarse râles at both bases with altered breath and voice sounds, especially on the right. The apex beat was in the fifth interspace, 8 cm. to left of the midline, and in the midclavicular line. Rhythm regular, pulse weak and thready. The temperature was 38° on admission and varied between 36.4° and 37.8° for the next five days. There were 14,400 W.B.C. with 74 per cent polymorphonuclears. Bedside X-ray at this time showed enlargement of the cardiac outline, with pulmonary congestion but no evidence of pneumonia. The patient for the first two days was in such a state of shock that the clinician thought it inadvisable to subject him to even the slight strain of electrocardiographic examination. He was given small doses of digitalis (2 grains a day) and showed improvement. On the fourth day (February 12, 1932) the E.K.G. (figure 2) showed a definite intraventricular block and a faint suggestion of an elevated *S-T* interval in the conventional leads. The P-A chest lead showed complete inversion of the *T*-wave, a very unusual finding in this lead. The complexes in the chest lead had changed so in the short period between January 25 and February 12, that one had to consider them as evidence of an active process taking place in the coronaries. An E.K.G. taken three days later, February 15, 1932 (figure 3) pointed again to coronary involvement, and showed for the first time a definitely elevated *S-T* segment in both Leads II and III; the P-A chest lead showed again marked changes in the low voltage *T*-wave.

With the rapid change in the complexes over the three week period, and finally with

the almost pathognomonic E.K.G. in all leads at the end of this period, the diagnosis of coronary occlusion could be made with definiteness, and was apparently corroborated by the later clinical course. At 2:30 the next afternoon, February 16, 1932, the patient suddenly developed a convulsive attack with stertorous breathing which rapidly changed to a Cheyne-Stokes type. The heart stopped; the breathing ceased soon after. In spite of medication he died within fifteen minutes.

The mode of death appeared very much like that seen in ventricular fibrillation.

COMMENT

From the electrocardiographic point of view the interesting fact in this case is that by use of the P-A chest lead coronary occlusion could be diagnosed with some definiteness at a time when no other evidence for it (except

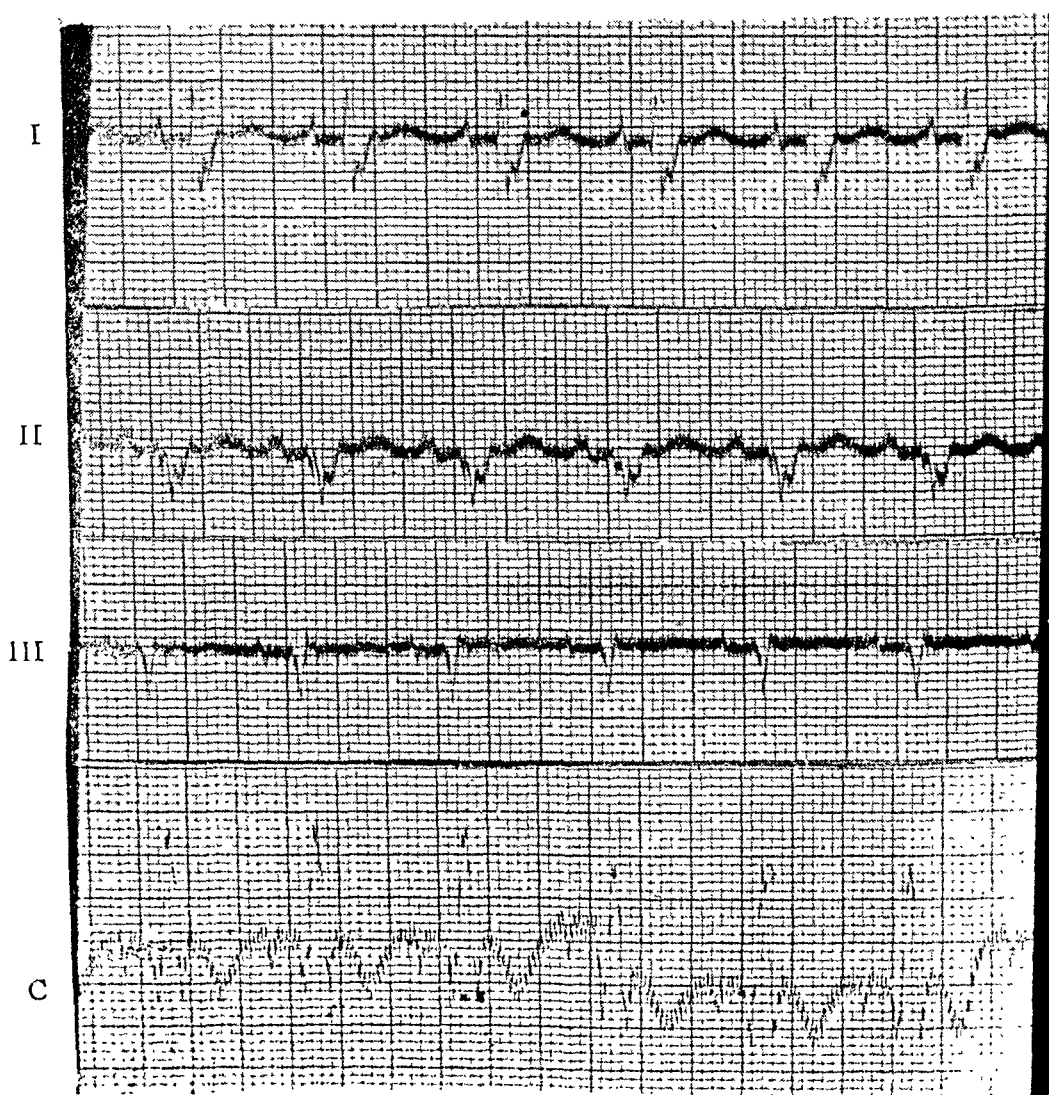


FIG. 2. (February 12, 1932). One week after an attack of pain in the epigastrium and chest, followed by leukocytosis (14,400) and a temperature of 37° - 38° C. Leads I, II, and III show intraventricular block, but no definite change in the S-T interval, while the Posterior-Anterior chest lead shows marked inversion of the T-wave—an extremely rare occurrence in this lead. The fact that this graph differs so from the former one would indicate that we are dealing with an acute process—coronary occlusion.

perhaps falling blood pressure) was present. The early findings in the conventional leads were quite insufficient to warrant such a diagnosis. When car-

possible to demonstrate in all leads an *S-T* interval abnormal enough to definitely indicate coronary occlusion. When this occlusion took place is hard

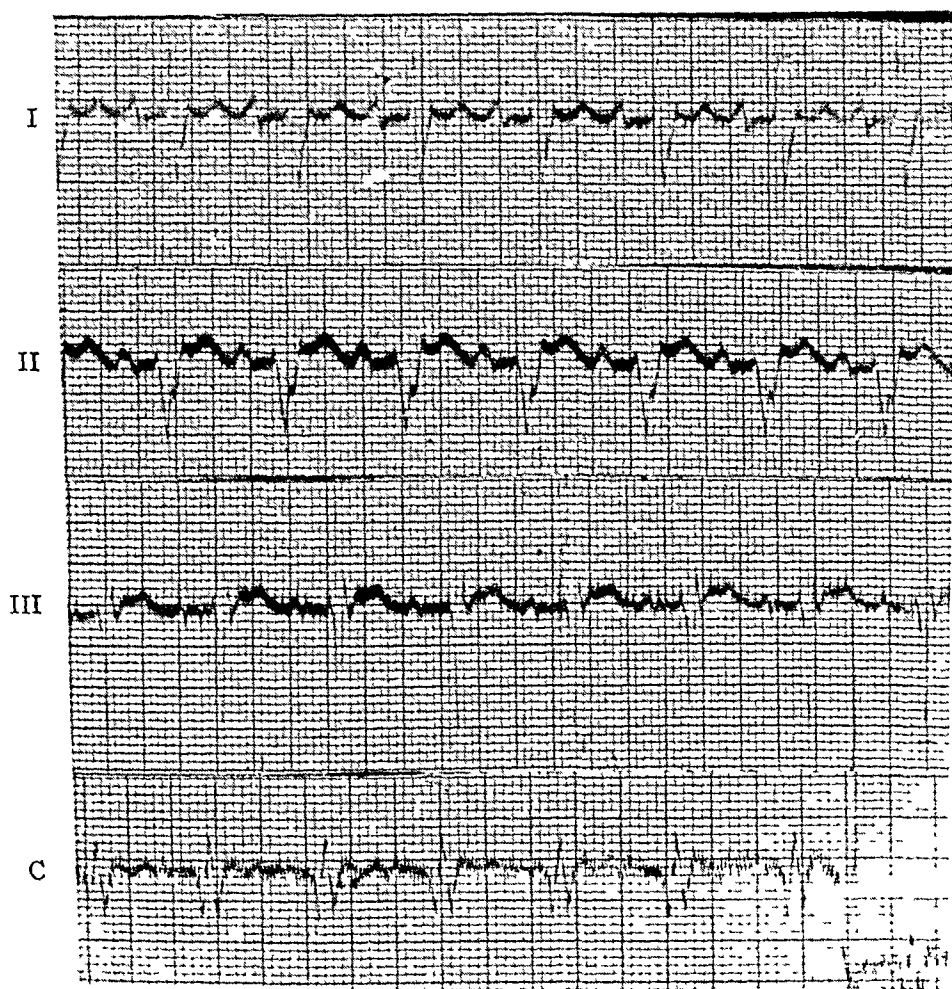


FIG. 3. (February 15, 1932). Taken three days after figure 2. There is a definite elevation of the *S-T* segment in Leads II and III. The conventional leads have assumed the typical aspect of recent coronary infarction. The Posterior-Anterior chest lead also shows marked changes from the previous tracing.

diac symptoms appeared, the P-A chest lead showed clearly those manifold rapid changes in the ventricular complexes that are so suggestive of coronary occlusion. It was not until the day before death, however, that it was

to say from either the history or the tracings, but in the first E.K.G. (January 25, 1932) there is already definite evidence (in the P-A chest lead) of coronary occlusion (possibly a slow closure); while the sudden attack of

epigastric pain and beginning decompensation of February 5, with the subsequent electrocardiographic evidence of acute coronary closure in the con-

ter), the "Right Arm" electrode being placed along the medial edge of the spine of the right scapula (about the level of the third dorsal spine), the

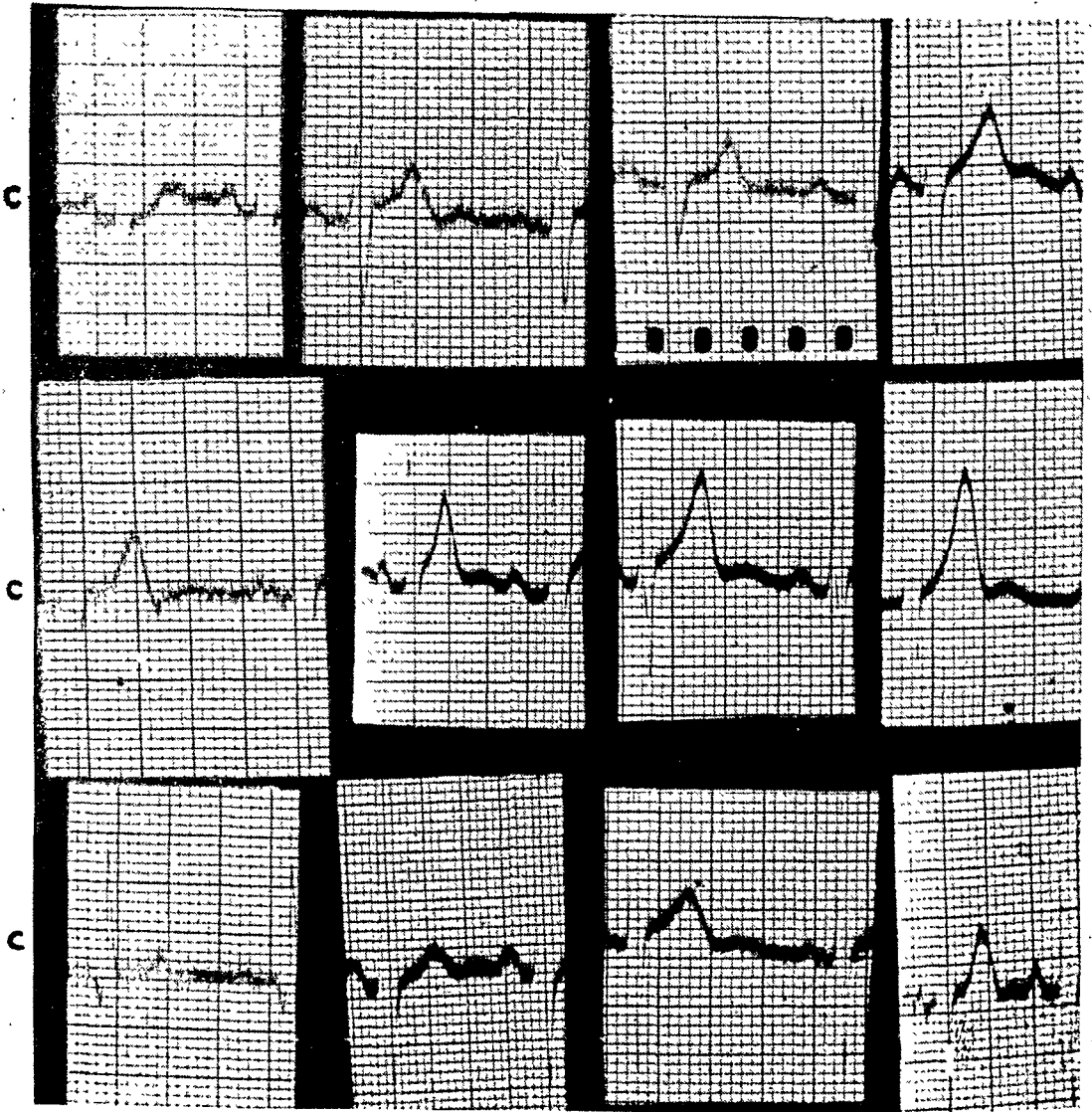


FIG. 4. Several examples of normal findings in the Posterior-Anterior chest lead, either in normal individuals, or in cardiacs showing normal electrocardiograms. Note that *P* is upright; *Q-R-S* diphasic and relatively large; the *u*-waves are prominent. The *T* take-off is never elevated more than 3 millimeters. Perhaps most important is the symmetry of the *T*-wave.

ventional leads, is especially suggestive of a recent thrombosis.

The technic used in obtaining the chest leads consists of the application of small, wet, gauze-covered copper electrodes (about one inch in diame-

"Left Arm" electrode going to the cardiac apex area. Great care is taken to avoid undue resistance by keeping the saline solutions warm, cleansing the skin thoroughly, and rubbing it lightly with a very fine copper wire

brush before applying the burnished electrodes. The string is carefully standardized before the taking of each lead; and no tracing is considered satisfactory that shows appreciable overshooting.

Thus far the electrocardiograms of 75 individuals have been taken, showing all four leads. Of these, 55 were cardiac suspects (5 of whom were cases of coronary damage) and 20 were normals. By a study of these normals it was found that the Posterior-Anterior chest lead is not less constant than the conventional leads. It shows characteristically a small up-right *P*-wave; a biphasic *Q-R-S* of high amplitude; a relatively large, up-right, symmetrical *T*-wave; and an *S-T* take-off of no more than 3 mm. elevation above the isoelectric line. The *u*-waves are usually prominent. A number of typical tracings of the Posterior-Anterior chest lead are shown in figure 4, and indicate the usual range of variation in this lead. An asymmetrical or inverted *T*-wave is always abnormal. The most constant finding in an acute coronary closure is a high *S-T* take-off with resultant asymmetry of the *T*-wave. This finding in the Posterior-Anterior chest lead may precede similar changes in the

other leads by days or weeks. This would tend to indicate that the axis of this chest lead is so situated as to register more surely the lesions produced by cardiac infarction. We believe, therefore, that the Posterior-Anterior chest lead is of definite clinical value.

CONCLUSIONS

A case is presented where marked *S-T* interval elevation was seen in the Posterior-Anterior chest lead fully three weeks before similar changes in the conventional leads. This permitted the diagnosis of coronary occlusion in the absence of any other definite sign. The further course of the illness and the later electrocardiograms appear to have substantiated this diagnosis.

Twenty normal individuals were studied to determine the normal range of variation in the Posterior-Anterior chest lead. This information helped substantially in the diagnosis of coronary involvement, which was made in five out of fifty-five cardiacs examined.

We wish to express our indebtedness to Medical Director M. H. Foster, in charge of the U.S.P.H.S. Hospital, Stapleton, S.I., for the privilege of using the hospital records, and to Assistant Surgeon S. P. Cooper, in charge of the Medical Service, for his kind cooperation in obtaining the electrocardiograms.

BIBLIOGRAPHY

¹WALLER, A. D.: A demonstration on man of electromotive changes accompanying the heart's beat, Jr. *Physiol.*, 1887, viii, 229-234.

²LEWIS, T.: Auricular fibrillation and its relationship to clinical irregularity of

the heart, *Heart*, 1909-1910, i, 306-372.

³WOLFERTH, C. C., and WOOD, F. C.: The electrocardiographic diagnosis of coronary occlusion by the use of chest leads, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 30-35.

Localized Atrophy of Subcutaneous Fat Following Repeated Injections of Insulin*†

Report of a Case

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THE localized atrophy of subcutaneous fat following repeated injections of insulin was first described by Depisch¹ in 1926, and since then has been reported by Barborka,² Davison,³ Mentzer and DuBray,⁴ Carmichal and Graham,⁵ Chapman,⁶ Rabinowitch,^{7,11} Lawrence,⁸ Priesel and Wagner,^{9,17} Avery,¹⁰ Fischer,¹² McCormick and Moorhead,¹³ Stransky,¹⁴ Price,¹⁶ Boller,¹⁸ Eeg-Olofsson,¹⁹ and Williams.²¹ Less than sixty cases are recorded in the literature, and of these, less than half are described even briefly, and only two biopsy reports are given.

The atrophy noted was almost always at sites of frequent insulin injections and began several months to several years after starting the injections of insulin into the areas later affected. It always involved the subcutaneous fat but produced no apparent changes in the skin or in the underlying muscles. The condition was more common in females than in males, and apparently was not related to the age of the patient, the duration of the diabetes nor to its severity, nor

to the make or amount of insulin used, nor to the methods used in sterilizing syringes and needles. Fischer¹² found the condition present in two-thirds of a group of diabetic children taking insulin. Depisch¹⁵ states that about 10 per cent of patients taking insulin have localized atrophy of subcutaneous tissues at the sites of injection. In one case described by Priesel and Wagner,¹⁷ the fatty atrophy was apparent only after the boy began to gain weight, there being no deposits of fat in the areas frequently used for the injection of insulin. Chapman⁶ reported a patient in whom fat returned in the areas of atrophy, these areas appearing normal two and a half years after discontinuance of the use of insulin. Various other authors report partial return of the fat. Boller¹⁸ and Stransky¹⁴ report a case where the atrophy of fat was noted at the areas of repeated insulin injections and also in one cheek where no injections had been made. The fatty atrophy of the cheek was treated by weekly procaine injections into the area, and three and a half months later the cheek appeared almost normal. Some of the patients experienced pain on the injection of insulin, but many did not. Boller be-

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lieves that if procaine is injected with the insulin no pain will occur and no fatty atrophy will result from its use.

Various theories have been advanced to explain the disappearance of the subcutaneous fat. Rabinowitch⁷ was unable to demonstrate the presence of lipase in insulin as a possible cause. Priesel and Wagner⁹ believe that the tricresol used in preserving insulin is the cause, but Depisch¹⁵ gave daily injections of tricresol solution for over two months without producing a fatty atrophy. Avery¹⁰ believes the subcutaneous fat atrophy is a nonspecific reaction, the result of repeated small traumata to the panniculus adiposum. Fischer¹² considers the most plausible explanation to be a low grade inflammatory process set up by repeated injections of insulin, the resultant damage causing replacement of the soft areolar tissue by scar tissue. He also considers the possibility that insulin may raise the level of local tissue metabolism, and thus eventually lead to the disappearance of fat by oxidation. Depisch¹⁵ believes that insulin causes injury to the nerve fibers. Williams²¹ thinks that insulin may injure the membrane that covers the fat cells, releasing fat globules, which, acting as foreign bodies, result in the formation of histiocytes which take on lipophagic activity.

Mentzer and DuBray⁴ report that sections from biopsy of the lesion show no lymphocytic foci and no evidence indicative of inflammatory changes. Eeg-Olofsson¹⁰ on microscopic examination found most of the change to be due to an ordinary atrophy of fat tissue, but that occasionally small areas of round cell infiltration

were found around the vessels. He found nothing which threw light on the origin of this atrophy of the fat tissue.

CASE REPORT

Patient M.B., thirty-two year old American woman, was first admitted to the University Hospital March 20, 1929, at which time she complained of weakness and dizziness of two months' duration and a loss of twenty pounds during this period. Physical examination showed evidence of some recent loss of weight, mild neuroretinitis, a slight diffuse enlargement of the thyroid, and a barely palpable liver and spleen. Urine showed 4 plus sugar and 2 plus diacetic acid. A diagnosis of diabetes mellitus was made and she was placed on a diet of 55 gm. protein, 220 gm. fat and 65 gm. carbohydrate with insulin as needed, the dosage varying from eight to seventy units daily. She was advised to continue the diet and insulin after discharge. On April 21, 1932 she was brought into the University Hospital in diabetic coma, having taken more food than her diet allowed and not having controlled with insulin her glycosuria of several months' duration. She was given large doses of insulin, recovered from the coma, and after a stay of about two weeks' duration was discharged on a diet similar to that prescribed before, with fifteen units of insulin twice daily.

In March 1931, about two years after starting to use insulin, she noticed disappearance of the subcutaneous fat in the anterior and lateral aspects of the upper arms, which were the areas where the insulin had been injected. In March 1931 she stopped using the arms as sites of injection and began using the anterior parts of the thighs. About six months later fatty atrophy began to occur in the anterior parts of the thighs and has been progressive since then. During the last year the fatty atrophy of the left arm has tended to diminish slightly. The accompanying photographs illustrate the extent of the fatty atrophy. In the depressed areas muscle could be felt beneath the skin, there being no evidence of fat at these points. Sensation was entirely normal and there was

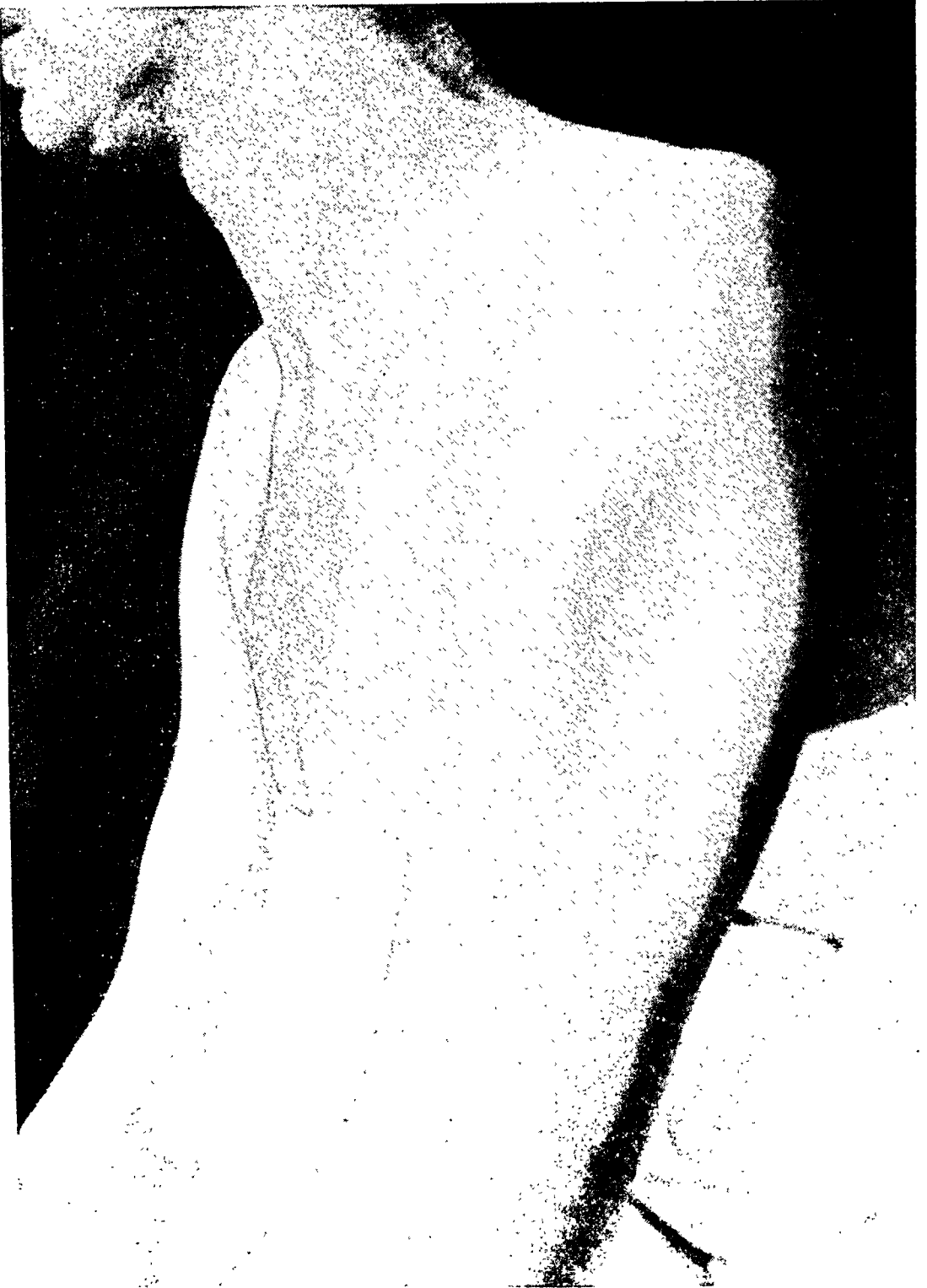


FIG. 1

no loss of muscle power. No pain had been experienced from the injections of the insulin which had been made repeatedly in the same areas.

Biopsy was done, a piece of skin and subcutaneous tissue being removed from the affected area on the anterior part of the

is an increased number of small blood vessels, some with slight thickening of the walls, and there is a slight perivascular lymphocytic infiltration. Some of the involved fat cells contain a small amount of albuminous material, but there is no evidence of fatty acid crystals or of soap formation"



FIG 2

right thigh. This was examined in the pathology laboratories of the University Hospital, and Dr. Carl V. Weller has been kind enough to furnish the following report. "The pathological changes resulting in the local atrophy in this material are confined to the panniculus. In the involved lobules the adipose tissue cells are very small and collapsed with a marked reduction in the total lipid content. With this change there

SUMMARY

A case of localized atrophy of the subcutaneous fat following repeated injections of insulin has been described.

Although the actual mechanism that causes the disappearance of the subcutaneous fat is not known, the condition seems to be associated with

frequent injections in localized areas, and, to prevent the condition it would be advisable to scatter the doses of insulin over as large an area of the body as possible.

BIBLIOGRAPHY

- ¹DEPISCH, F.: Über lokale Lipodystrophie bei lange Zeit mit Insulin behandelten Fällen von Diabetes, *Klin. Wchnschr.*, 1926, v, 1965-1966.
- ²BARBORKA, C. J.: Fatty atrophy from injections of insulin, *Jr. Am. Med. Assoc.*, 1926, lxxxvii, 1646-1647.
- ³DAVISON, R. A.: Absorption of subcutaneous fat deposits at site of repeated insulin injections; report of a case, *Calif. and West. Med.*, 1927, xxvi, 210-212.
- ⁴MENTZER, S. H., and DUBRAY, E. S.: Fatty atrophy from injections of insulin, *Calif. and West. Med.*, 1927, xxvi, 212.
- ⁵CARMICHAEL, E. A., and GRAHAM, G.: Local fat atrophy following insulin injections, *Lancet*, 1928, i, 601.
- ⁶CHAPMAN, P. D. H.: Local fat atrophy following insulin injections, *Lancet*, 1928, i, 674.
- ⁷RABINOWITCH, I. M.: Atrophy of subcutaneous fat following insulin injections, *Canad. Med. Assoc. Jr.*, 1928, xviii, 560-561.
- ⁸LAWRENCE, R. D.: Effect of prolonged use of insulin on the subcutaneous tissues, *Lancet*, 1928, i, 1328.
- ⁹PRIESEL, R., and WAGNER, R.: Über lokale Lipodystrophie nach Insulininjektionen, *Ztschr. f. Kinderh.*, 1928, xlv, 453-456.
- ¹⁰AVERY, H.: Insulin fat atrophy—a traumatic atrophic panniculitis, *Brit. Med. Jr.*, 1929, i, 597-599.
- ¹¹RABINOWITCH, I. M.: Case of extensive atrophy of subcutaneous fat following injections of insulin, *Canad. Med. Assoc. Jr.*, 1929, xxi, 67-68.
- ¹²FISCHER, A. E.: The frequency of atrophy of the subcutaneous fat following the injection of insulin, *Am. Jr. Dis. Child.*, 1929, xxxviii, 715-720.
- ¹³MCCORMICK, V. O., and MOORHEAD, T. G.: Insulin fat atrophy, *Irish Jr. Med. Sci.*, 1929, 727.
- ¹⁴STRANSKY, E.: Lipodystrophie um die und fernab von den injektionstellen nach Insulinbehandlung bei Diabetes mellitus, *Wien. med. Wchnschr.*, 1930, lxxx, 133-134.
- ¹⁵DEPISCH, F.: Weiterer Beitrag zur Frage der lokalen Lipodystrophie bei Dauerinsulinbehandlung, *Wien. med. Wchnschr.*, 1930, lxxx, 168-169.
- ¹⁶PRICE, L. R. W.: Local absorption of fat due to injections of insulin, *Lancet*, 1930, i, 1015-1016.
- ¹⁷PRIESEL, R., and WAGNER, R.: Die Insulinlipodystrophie bei Kindern, *Klin. Wchnschr.*, 1930, ix, 1548-1549.
- ¹⁸BOLLER, R.: Behandlung der Insulin-Lipodystrophie, *Klin. Wchnschr.*, 1930, ix, 2433-2435.
- ¹⁹EEG-OLOFSSON, R.: Local changes in subcutaneous tissue following injections of insulin, *Acta med. Scandinav.*, 1930, lxxiii, 89-98.
- ²⁰DEPISCH, F.: Über lokale Lipodystrophie, Bemerkungen zur Arbeit von Priesel und Wagner "Die Insulinlipodystrophie bei Kindern", *Klin. Wchnschr.*, 1931, x, 1174.
- ²¹WILLIAMS, J. R.: Case report of extensive atrophy of subcutaneous fat following repeated injections of insulin, *Jr. Lab. and Clin. Med.*, 1931, xvi, 1191-1193.

Primary Spondylitis*†

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IN approaching the study of spondylitis, or arthritis of the spine, one may properly ask that its relation to the large group of chronic arthritide be defined.

Any discussion of chronic arthritis is at present most confusing because of the numerous classifications and the many variations in terminology. Classifications now in use are, in general, based upon etiological or pathological suppositions. Etiological classifications can be of little help, as no single factor has definitely been proved to be the specific causative agent. One needs to recall but a few of the present affirmed etiological factors to realize that chronic arthritis is as yet a disease of unknown origin. The neurogenic theory, the theories of vascular deficiency, trauma, endocrine deficiency, presenile changes, disturbed metabolism, infection, and many other hypotheses all have ardent supporters. Pathological groupings are but little better as material is very difficult to secure at progressive stages, and scattered observations during different stages of the same disease are apt to be misleading. The number of pathological examinations that have been correlated with

clinical studies are far too few upon which to base an opinion. One of us (W.P.H.) has asked many pathologists in this country and abroad for such information only to be told that the pathologist's interest lay elsewhere, or that insufficient material could be secured to be of any value.

It has been a hopeless task from our standpoint to fit our arthritis patients into existing ready-made groups. During several recent medical conferences in which arthritis was a special interest, leading authorities have proposed more than a dozen separate classifications and have recommended equally diversified treatment. Because of this existing confusion and the absence of uniform clinical concepts, we decided to study a large group of arthritics completely and uniformly. These studies were made under the most complete control and supervision of the patient and in ideal climatic surroundings. During the past eighteen months three hundred patients with chronic arthritis have been selected from our hospital and outpatient department for this study. We have tried to consider these patients from two standpoints. We have attacked the problem as a research which involved many exhaustive tests and examinations. But we have also attempted the simplest clin-

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BIBLIOGRAPHY

- ¹DEPISCH, F.: Über lokale Lipodystrophie bei lange Zeit mit Insulin behandelten Fällen von Diabetes, *Klin. Wchnschr.*, 1926, v, 1965-1966.
- ²BARBORKA, C. J.: Fatty atrophy from injections of insulin, *Jr. Am. Med. Assoc.*, 1926, lxxxvii, 1646-1647.
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- ⁴MENTZER, S. H., and DUBRAY, E. S.: Fatty atrophy from injections of insulin, *Calif. and West. Med.*, 1927, xxvi, 212.
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ical approach, and it is this practical clinical study that is responsible for the grouping shown in table 1.

The average length of time these patients were under observation was slightly over five months. Many of them were in the hospital the entire time, and nearly all of them were hospitalized at intervals. This group of patients has been carefully analyzed as to history, physical examination, laboratory, roentgenologic studies, and response to treatment. We have not assumed any specific etiology but have grouped them solely upon a clinical basis.

The greater portion of our patients come from widely separated points geographically, and so should represent an accurate cross-section of types. It is only fair to say that most of them are "last-resorters", and so should be thought of as representing the very chronic or advanced stage of the disease.

It seemed at the beginning an endless task, but there have emerged to date six well defined groups. No argument is being made at this time for a separate etiology. Indeed it is wholly possible that several groups may have one or many etiological factors in common. We have, however, found such a grouping practical and very helpful in selecting therapeutic measures; table 1 presents a brief analysis of the six groups.

Group I is an afebrile, insidious, progressive, symmetrical, deforming, and crippling disease. Arthritis deformans, rheumatoid arthritis, atrophic arthritis, and proliferative arthritis are other common terms loosely applied to any severe polyarthritis. This group is

separated from Group II, which appears infectious in its manifestations, because of Group I's marked predilection for women beyond the third decade, its symmetry, the lack of fever, the marked and wide-spread demineralization, the early cartilage destruction, the trophic skin and muscle changes, and the complete failure of therapy when directed toward infection or when the problem is attacked solely from the standpoint of foci of infection. It is a disease often dramatically affected by the patient's emotional life, and in most instances is associated with some form of gastrointestinal dysfunction. If infection plays a major rôle in this group of cases, its manifestations are not obvious, and there are surely other necessary factors.

Group II Arthritis is most commonly termed chronic infectious. It is also known as atrophic, or rheumatoid, and is referred to in many other terms. It is in general not separated from Group I. In contrast to Group I, however, there is fever, malaise, and other constitutional symptoms of infection. Everyone is familiar with this picture of infectious polyarthritis with pain, heat, redness, and swelling in the joints at some stage of the disease and usually at the onset. In this most acute phase it is with difficulty that it is differentiated from acute rheumatic fever.

Group III Arthritis is often classified as osteoarthritis, hypertrophic arthritis, degenerative arthritis, and streptococcus viridans arthritis. This is a disease which comes on rather late in life with insidious onset, and usually first noted because of stiffness of the spine or fingers. Heberden's nodes

TABLE I
CLINICAL GROUPING

	I	II	III	IV		V	VI
				SPONDYLITIS			
				(A) M Only	(B) M Only		
Sex	5F-1M	2M-1F	5M-1F			1F-1M	2M-1F
Age Onset	30-50	Any Time	Late	20-30	20-40	40+	Any
Pos. Hist. Before Onset ..	Psychic Constip.	Head Infection	None	Fatigue Constip.	Severe Infection	None	Infection
Onset Ac. or Insid.	Insid.	Acute	Insid.	Insid.	Either	Insid.	Acute
First Joint	Prox. Phalang.	Any	Spine Fingers	Spine	Spine	Wt. Bearing	
Joints Invol.	Peri.	Peri.	Any	Spine	Spine		
Joints P.H.R.S.	P.-S.	P.-H.-R.-S.	P. and S.	P.-	P.-	P.-S.	P.-
Deformity	Yes-Char.	Not Char.	No	Yes-Char.	Yes	Occ.	No
Symmetrical	Yes	No	No	Yes	Yes	No	No
Trophic Skin and Muscle	Yes	Not Early	No	No	No	No	No
Wt., Gen. Health	Good	Reduced	Good	Reduced	Reduced	Good	Good
Const. Type	3 or 4	Any	1 or 2	3 or 4	Any	1 or 2	Any
B. P.	Low	Any	Up	Low	Any	No-Up	Normal
Heart Lesion	No	Often	No	No	No	No	No
Foci	No	Yes	Not Marked	Not Marked	Not Marked	No	Yes?
Other Pos. Findings	Seldom Any	Often Many	Seldom Any	Seldom Any	Many	Over-weight	
Fever-Onset-Course	No-Low	Yes	No	No	Occ.	No	No
Treatment	Diet Exercise	Foci Vaccine	General	Diet Posture	Foci General	Reduce Posture	Foci General
LAB.	RBC & HB ...	Normal	Anemia	Normal	Sl. Anemia	Normal	Normal
	WBC-Diff. ...	Normal	High	Normal	Normal	Up-Normal	Normal
	Sedimentation..	Rapid	Rapid	Normal	Rapid	Increased	?
	Gastric HCl	Low-Absent	Normal	Normal	Low-Absent	Normal	Normal
	BMR	Normal	Normal	Normal	Normal	Low	Normal
	Periart.	Yes	Yes	No	No	No	Yes?
X-RAY	Cartilage	Yes-Early	Yes-Late	No	No	No	Yes
	Bone	No	Yes-Late	Yes	No	Yes	No
	Demineral. ...	Yes-Early	Not Early	No	No	No	No
	G.I. Tract ...	Colon	Sigmoid	Normal	Colon	Sigmoid	Normal

often occur, and there is usually only pain and swelling of the joints without heat or redness. The weight and health are excellent. The blood pressure is normal or elevated, and the constitutional type tends toward the sthenic. It is relatively a benign disease producing lipping and spurring in various joints.

Group IV is the group of primary spondylitis which we will discuss shortly.

Group V is often referred to as metabolic, traumatic, or menopausal. The important factor in this group is that a weight-bearing joint, usually a hip or a knee, is involved. Ordinarily, not more than one or two joints are affected, and this is one respect in which it differs from Group III osteoarthritis which is a generalized disease. Patients of Group V are usually overweight with no significant findings except in the weight-bearing joints or in joints that have suffered trauma. The riding master with an arthritis of the hips, the watch-maker with involvement of the cervical vertebrae, and the trap-shooter with arthritis of the shoulder are included as well as the overweight, middle-aged woman with painful knees.

Group VI may properly be termed pre-arthritic and in it are included all manifestations of neuritis, myositis, bursitis, and fibrositis.

We have included spondylitis for purposes of simplicity in grouping as one of the groups of chronic arthritis. Primary chronic arthritis of the spine represented by Group IV may be separated into two general groups: Type A (without bony ankylosis), and Type B (with bony ankylosis). The lipping

and spurring of the spine seen commonly with generalized osteoarthritis is not included in this grouping but it is included under the generalized disease of Group III. It should be clearly understood that this discussion is limited to what may be properly called primary spondylitis as manifested by a painful rigid spine. In reviewing the last three hundred patients seen with chronic arthritis, twenty-two cases of primary arthritis of the spine were found. Thus over 7 per cent of the total three hundred suffered from primary spondylitis. Of the twenty-two, ten were Type A (without bony ankylosis), and twelve were Type B (with bony ankylosis). These cases of spondylitis are briefly tabulated in tables 2 and 3.

Type A spondylitis, (table 2), is an unusual disease, or more probably an unrecognized syndrome, for we have found no description of this condition in the literature. Most remarkable is the observation that only males have been seen with this disease. The age of onset is in early adult life from seventeen to thirty. The duration of the disease has varied from one to sixteen years and has averaged six and nine-tenths years. All patients of this group are still alive and under periodical observation. The onset is insidious and gradually progresses to a poker spine. There is much pain and muscle spasm in the back. The patient walks with a peculiar waddle characteristic of a fixed spine and pelvis, exaggerated no doubt by adductor muscle spasm in the thighs. Dyspnea on exertion is the rule because of fixation of the rib cage. Chest expansion is often scarcely perceptible. The head is us-

TABLE II
SPONDYLITIS (Type A)

	R.C.R.	J.R.	C.B.S.	J.C.R.	W.N.J.	E.A.S.	R.W.	R.B.	H.F.*	I.H.*
Sex	M	M	M	M	M	M	M	M	M	M
Age	30	33	44	27	30	37	31	22	37	29
Age Onset	25	28	28	26	26	30	26	17	24	21
Onset, Ac. or Insid.....	Insid.	Insid.	Insid.	Insid.	Insid.	Insid.	Insid.	Insid.	Insid.	Insid.
Const. Type	III	III	IV	IV	IV	II	III	III	IV	III
Gen. Health	Poor	Poor	Poor	Fair	Poor	Fair	Poor	Poor	Poor	Poor
Weight Loss	30	30	43	11	70	15	22	20	25	46
Joints Invol.	Spine	Spine	Spine	Spine	Spine	Spine	Spine	Spine	Spine	Spine
Rigid Spine	Yes	Yes	Yes	Yes	Yes	Mod.	Yes	Mod.	Yes	Yes
Deformity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
B.P.	110/65	103/80	126/80	120/90	112/68	148/80	110/70	110/80	112/80	100/70
Foci	None	GB?	None	None	None	None	TB	None	None	None
Fever	None	None	None	None	None	None	None	None	Yes	None
RBC & HB	N	N	N	N	N	N	N	N	Low	N
WBC-Diff.....	N	N	N	N	N	N	N	N	N	N
Sed.-RBC	Rapid	Rapid	Rapid	Rapid	Rapid	Rapid	Rapid	N	Rapid	Rapid
BMR	N	N	N	N	+25	N	N	N	N	N
X-Ray	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

*These two patients later developed acute polyarthritis without any change in the spine condition and with all manifestations of Group II Arthritis.

usually carried slightly forward and tends to produce a dorsal kyphosis with a loss of lumbar curvature. The constitutional type involved is the asthenic individual. The general health is poor and the patient shows evidence of a severe constitutional disease. Loss of weight is often marked, and in our series varies from fifteen to seventy pounds. The spine alone is usually involved, although muscle spasm in the back in most cases produces limitation of motion as well as pain in the shoulders and hips. In spite of evidences of severe constitutional disease with marked fatigue, loss of weight, and pain and stiffness in the spine, there is no fever, no anemia, no leukocytosis, and no obvious infectious foci in the majority of these patients. Most astonishing, however, is the absence of demonstrable roentgenologic changes in these completely stiff spines. One of this group has had the disease for nearly sixteen years, having much pain with rigidity of the spine, and as yet the spine shows no demonstrable bony ankylosis. All of the patients show an unusual roentgenologic appearance of the sacroiliac joints. There is loss of cartilage and presumably fusion. Very complete studies have been done on these patients but only a brief summary can be given here. These patients are alike as peas in a pod. No one can fail to recognize the picture when familiar with it. Patients who suffer from this disease are so identical in their many manifestations and so different from other types of arthritis that we have felt justified in considering Type A spondylitis as a separate disease syndrome.

Type B spondylitis (table 3) is

characterized by stiffness of the spine associated with bony bridging between the vertebrae. The bridging may be local or generalized to include the entire spine. It may be associated with involvement of the hips and shoulders, and there is often ossification of the ligamentous attachments of muscles about the pelvis. The condition described by Knaggs as *Spondylitis Ligamentosa Ossificans* may be identical and the term is undoubtedly a good descriptive one for this group of cases. This striking picture must not be confused with the benign lipping and spurring so frequently seen in the spines of Group III Osteoarthritis. Type B spondylitis differs from Type A in several interesting respects, although the patients do not appear widely different on casual examination. Again, these patients are limited to the male sex. The average age and the age of onset are quite similar to the Type A cases. The character of the onset, however, is often acute, with a febrile illness, while the insidious onset is distinctive of Type A. The constitutional type, the general health, and the weight loss are not particularly different from Type A. Several of these Type B patients gave a history of one or more peripheral joints having been involved. Foci of infection are frequent in this group of patients and exceedingly rare in Type A. Attention must be called to the frequency with which tuberculosis occurs in the Type B group. Seven patients out of a total of twelve had presumptive tuberculosis. Fever is the rule in this group, while but one patient in the Type A group had fever and that only with occurrence of an acute infection.

Anemia and leukocytosis occur more frequently in Type B than in Type A. However, the most startling difference between the two groups is in the roentgenologic findings. Type B shows massive bridging of the spine with calcification of ligaments, and many times this extends to the muscle attachments about the pelvis. The Type A patients reveal absolutely nothing to account for the rigidity of the spine.

To find twenty-two men with stiff, rigid, and painful spines among the three hundred routine chronic arthritics studied was something of a surprise. We have since gone over all the additional patients possible in search of a female with this disease, but up to the present time have not found one. This seems more significant, because of the three hundred arthritics studied more than half were women. The men of both groups were all afflicted in the prime of life, and nearly all of them had lived sheltered and protected from physical strain. Physicians, dentists, lawyers, and accountants were frequently victims. This spondylitis should not be confused with the condition ordinarily known as "laborer's spine". The pain and discomfort suffered by patients with Type A spondylitis is not unlike a severe and permanent lumbago, if one can imagine such an unhappy afflic-

tion. Coughing or sneezing may produce the most agonizing pain as well as marked intercostal muscle spasm. The Type B patients get much relief from pain when the ankylosis becomes complete and many of them reach an entirely painless stage in which their major discomfort is limitation of motion. Complete case reports, together with a discussion of etiology, treatment, and prognosis will appear shortly in a more detailed paper.

SUMMARY

1. Two specific types of primary chronic spondylitis occurring only in males are reported,—one with bony bridging, and one without bony bridging. The twenty-two cases reported represent 7 per cent of the three hundred patients with chronic arthritis studied.

2. The Type A spondylitis without bony bridging is emphasized as being a clinical entity not usually recognized and about which little has been known. The surprising frequency of this condition warrants its consideration in the diagnosis of every young man with back pain.

3. A clinical grouping of chronic arthritis based upon similarity of clinical findings is given to present the relationship of spondylitis to this grouping.

The Teaching of Inheritance of Disease to Medical Students*

A Proposed Course in Medical Genetics

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GENETICS has made greater strides in the last twenty-five years than any other of the biological sciences. So exact has this study become that the position of the ultimate determiner of hereditary characters is plotted on a chromosome map with the same exactitude with which the explorer denotes the geographical position of any given place on the earth's surface. With such an increase in knowledge, it is inevitable that an application of genetics to man should be made. Because it is much easier to trace the hereditary wanderings of some *peculiar* character through a human pedigree than it is to follow the trail of normal characters that are so common that they are universal, the study of human heredity has largely centered about pathological conditions.

This interest in pathological heredity has been enhanced to a certain extent by the fact that the brilliant work done in preventive medicine by the immunologists and sanitation experts has served to decrease very materially the death rate from infectious diseases. Persons spared from death by infection are kept alive to succumb to their constitutional disorders, so that we

find the death rate from many of the degenerative disorders of the circulatory system, from cancer and from diabetes, rising. As many of these constitutional ills have an hereditary background, the triumphs of modern preventive medicine have served to throw into stronger relief the problems of human inheritance.

The medical profession as a whole has a very limited conception of how many diseases are inherited. It is true that many of them are rare, fortunately so, and that they do not bulk as large in numerical importance as do the infectious diseases, but being inherited they increase alarmingly as the years go by. From the standpoint of financial burden to the public, the whole public health program probably does not cost the people as much as do the hereditary diseases of the nervous system alone, with their schools for the feeble-minded, institutions for the insane, special schools for the blind and deaf, etc.

Premedical Training. The biologist who trains the medical student in his premedical days does much to stimulate interest and to instruct the student in the fundamentals of genetics. Unfortunately, however, most students

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are not able to see the value of this work, because the illustrations given them of necessity deal so largely with plant and animal life, usually animal life of a relatively low order. The information gained is thus apt to seem almost wholly dissociated from the realm of human disease, which is to be the practitioner's life work.

Even if the biologist were to give examples from pathological inheritance in man, the student is not yet sufficiently advanced to understand either the terminology or the significance of the illustrations used. One cannot make inheritance in Friedreich's ataxia mean anything to a student, when he has no idea of what Friedreich's ataxia is, what a knee jerk is, what claw foot is, etc. The student can absorb only so much at a time. The biology course should not include clinical subjects; it should give the student training in the fundamentals of genetics, so that when he comes to his clinical work the terms used in the discussion of inherited diseases may be intelligible to him.

Necessity for Medical Training in Genetics. The formal teaching of genetics should, however, not stop with the course in biology. Much knowledge concerning the inheritance of disease has been accumulating which is of very practical importance to the practitioner; practical because it will increase his diagnostic acumen, his therapeutic skill, his prognostic ability, and will at the same time enlarge his opportunities for preventive work. This knowledge, it is true, has not been taught to the medical student in the past, except as it came in as an aside in the clinical lectures of some clinician particularly interested in heredity.

This lack of formal instruction in the past explains why many of our clinical teachers of today are not trained to bring the significance of heredity into their lectures. The students of today are receiving little information on the subject and as they become the clinical teachers of tomorrow, the lack of teaching in this branch will continue. For this reason we should have a definite course designed primarily to teach the student what is known of heredity in disease. It is true that not a great deal is known of some aspects of human inheritance, and that what we teach must be taught with many reservations. The same is true of many of the so-called facts of our medical knowledge of today. That does not deter us, however, from teaching what is known.

One of the greatest values accruing from the inclusion of such a course would be not so much the knowledge it gave to the particular students, as the knowledge they would ultimately give to us to correct our faulty notions and our incomplete observations. The student who is alive to the importance of heredity will observe and report accurately its manifestations in his patients. The student who never knew that diabetes and pernicious anemia were inherited will pass by the hereditary aspects of these diseases, because he will feel that it was by mere chance that several brothers and sisters were affected in one family. At a recent talk before physicians, I was astonished to find the numerous striking instances of inheritance of pathological conditions which even a group of only twenty-five men could recall from their practices. In some cases the knowledge

of the condition in other members of the family was of help in diagnosis. Thus they recalled a parent and two children with heart block; a man and his son operated upon for renal calculi; three generations of displaced lens; marked mental deficiency in mother and children; pernicious anemia running through several generations, etc. But none of these had ever crept into the clinical literature, because they had not seemed of sufficient importance. Yet we have those who are skeptical of the influence of heredity in disease, because there are so few published records of it.

I have said that a knowledge of inherited diseases would be of value from the diagnostic angle. It naturally follows that when the diagnosis is better, the therapeutic procedures that follow will be better and the results for the patient improved. Let me cite briefly two examples. So many relatively rare diseases come under the category of inherited diseases that, if they are not mentioned for their heredity value, the student may never hear of them. It is the rare disease that often gives the practitioner his chance to establish a reputation. For example, one roentgenologist advised removal of a child's arm for sarcoma of the humerus. The plate showed a growth, and sarcoma was the diagnosis. The family objected, and the child was sent elsewhere. The second physician showed not only a growth on the arm, but beginning growths elsewhere, and also similar bony excrescences in the father. A diagnosis of hereditary deforming chondrodysplasia was made and the child still has its arm.

A second child with very dry skin,

sparse hair, and only one tooth was treated as a hypothyroid case and given thyroid extract. The patient was not benefited, and finally was taken to another physician, who recognized that the mother had very few teeth and diagnosed the cases of both mother and child as hereditary ectodermal dysplasia. The child showed more extensive involvement than the mother. He recognized the futility, even the cruelty, of thyroid treatment. Here was a child with no sweat glands, who was already handicapped in the endeavor to keep his body cool, being given medication which whipped up his metabolism and thus increased his discomfort.

One has only to think of pernicious anemia, and the opportunities there for preventive therapy with members of the family who have not yet shown the anemia but who are in the achylic and achlorhydric stage, to realize that a knowledge of the inheritance of disease is important from the point of view of preventive medicine.

It seems evident, that information concerning heredity in disease should not be given to students until they have had some lectures dealing with the diseases under discussion, and until they have become familiar with the signs and symptoms of disease. The proposed course which would give to the student a knowledge of heredity in pathological conditions will be of most value to him only if it is given in the final year, when he is acquainted with the subjects of medicine and surgery and all their branches. This does not mean, however, that inheritance is to be ignored in other courses and given to the student only at the

end of his career. The more widely trained our teachers become, the more they will correlate their courses with the course in medical genetics. The student will receive his biological background in his premedical days. When he enters upon his course in embryology, which deals with human development utilizing chick and pig material only for the early stages, he constantly meets with the influence of inheritance. Thus maturation of the ovum and sperm can be made a matter of great fascination by illustrating it with records of inherited human diseases, showing how through maturation comes the opportunity for segregation of characters which we see so strikingly illustrated in human pedigrees. Discussion of the mode of formation of the uriniferous tubule can be made a theme of thrilling interest, by the discussion of polycystic kidney and its inheritance. A dozen malformations of the developing fetus, which serve to emphasize the manner of normal development, can be made real to the student, not only by cooperation with the staff of the children's hospitals, whereby cases can be brought into class, but also by discussion of the inherited factors behind these conditions. I have found my students more than interested in embryology, through which runs a constant thread of heredity not only of the normal but of the abnormal characters.

In gross anatomy, an anomaly found in the dissecting room can form the basis of a short talk on what is known of the inheritance of that particular condition. In physiology the discussion of the mechanism of urine secretion and of the threshold of excre-

tion for salts, sugar, etc., offers an opportunity for pointing out the hereditary factor in ortho-glycemic glycosuria. Pharmacology brings up hereditary peculiarities and idiosyncrasies to drugs. Biochemistry in teaching metabolism can point out the hereditary anomalies which allow certain persons to excrete alkapton, pentose, urobilin, or sugar.

In clinical fields, of course, opportunities are unbounded, and the value of a knowledge of inheritance to the physician who can thus get "diagnostic tips" is very real. The obstetrician who is having a hard time to deliver a woman whose pelvis is deformed through osteogenesis imperfecta and who has to resort to forceps in order to effect delivery may be able to save himself a suit for malpractice, if he brings into the world a baby with three or four fractures. Or if he has delivered a woman of one hydrocephalic child, he may be able to make the same diagnosis much more readily when the second shows the same defect, thus shortening the labor and modifying the technic employed to bring about birth.

The surgeon who is dealing with inguinal hernia, or with varicose veins, has opportunities for discussing the inheritance of these conditions. The pediatrician who has in clinic a baby with fatal jaundice can not only discourse upon the embryology of the formation of bile ducts, but upon the inheritance of that factor which inhibits the normal development of that minute part of the embryo, and so causes many babies in the same family to have the same disease. The neurologist has unlimited opportunities for

bringing out the inheritance factor in disease, and also for emphasizing the fact that knowledge of the presence of an inheritable disease in the family of the patient may be an aid to early diagnosis. Thus the mere diminution of a knee jerk, which might not be noticed ordinarily, becomes most significant when one knows that another member of the family had Friedreich's ataxia; or the enlarged limbs of a still healthy lad may assume a sinister meaning when we know that his older brother had pseudo-hypertrophic muscular dystrophy.

Thus all the way through the medical course the student would be learning of inheritance and of its importance in disease. Such instruction, however, would not remove the need of a course in medical genetics in the senior year. Such a course would round out the student's conceptions of the subject and would enable him to classify systematically the various manifestations of heredity as seen in clinical medicine. The senior student's clinical training would enable him to appreciate this course and to put the knowledge gained to use in his daily work. Even in such things as infectious diseases, he would learn that there are inherited immunities or partial immunities, so that the dark skinned races are less susceptible to skin infections and more susceptible to respiratory infections than are the light skinned races. He would learn that the children of one family respond to even the slightest irritant with a high fever, while in another family, the reaction is much less. He would see that some children have convulsions with a very low fever, while other children do not have convulsions even

with a very high temperature. All such facts he will correlate with the great hereditary complex that goes to make up an individual.

With such a background our students may return to that conception from which modern methods have somewhat deflected us; namely, to the conception of the patient as an individual, not merely a case for the surgeon, the gastro-enterologist, or the gynecologist, but an entity whose physical, mental, and metabolic background contributes to his disorder. More than that, the physician with training in medical genetics will begin to take a long term view of medicine and its preventive and public health aspects. He will not neglect the patient, but he will visualize him as an entity in society. He will not only cure his present ill, if possible, but he will be able to forecast some that may occur to him because of his makeup, and to forestall them.

By Whom Should the Subject Be Taught? The subject should not, however, be left entirely to those who are teaching in the various branches of surgery or medicine, for not infrequently they are not familiar with or interested in the topic. We do not leave the subject of roentgenology to be taught as an aside by the surgeon, even though the latter constantly uses and refers to X-ray pictures as an aid to diagnosis. Similarly, medical genetics should be taught by a medically trained person who is thoroughly conversant not only with the subject of medicine but with the field of genetics, who knows it as intimately as the gastro-enterologist or the roentgenologist knows his special field of diagnosis and therapy.

Medical genetics is a specialty, only

in the same sense that pediatrics, internal medicine, or gynecology are specialties. It touches the work of the practitioner in many intimate ways; as he becomes familiar with it his usefulness to the patient and to the community is increased. Knowledge of medical genetics is far more essential to the practice of medicine than is the carrying out of many of the elaborate experiments in the preclinical years, which are designed for the research worker in that particular branch of science rather than for the medical student. It might be thought that since medical genetics is an essential part of general medical knowledge the teaching of it could be confined to the clinicians who give instruction in the symptomatology, the physical signs, the diagnosis and therapy of disease. The fact cannot be ignored, however, that clinicians do not usually take advantage of their opportunity to give instruction in the inheritance of disease and largely this is because of lack of familiarity with the subject. The data are scattered and often buried in inaccessible clinical reports and so are not available for the preparation of a clinic. The clinicians teach what they know, and leave untaught what is not familiar to them. Of course there are brilliant exceptions. I cannot forbear to mention Dr. Lewellys F. Barker who never misses an opportunity of discussing the heredity of the disease shown in his clinic if there be an inherited background. For the most part, however, it will be necessary that a person with medical training and with particular experience and training in the study of inheritance in disease should be the one selected to

give the students instruction in this field.

It is true that the medical curriculum is over-crowded, but it was pointed out at a recent congress held at Edinburgh University, that the teaching of today is too largely permeated by the curative ideas of the medicine of yesterday rather than by the preventive ideas of medicine of today. It is in the field of prevention that medical genetics promises to be most useful. The meeting went on record as stating that the interest of the student was too largely directed to the end products of disease from the clinical angle, and to an unnecessary wealth of detail which had little or no bearing on his work as a practitioner on the preclinical side. The greatest need was for more applied biology (and what is more evidently applied biology than medical genetics) and also for more emphasis on prevention rather than on cure.

Opportune Time to Introduce Course in Medical Genetics. The time is ripe for the introduction of such a course into medical schools. The popularization of science by biology teachers and writers, the education of the public to some extent by physicians who are "heredity conscious", as well as by lectures, radio broadcasts and literature distributed by eugenic and genetic societies, are stimulating inquiries by the public which the physician must answer. If the medical schools do not recognize their opportunity and their obligation in this matter, the profession will be less well informed than is the laity. Medical courses should prepare the student for future needs; they should give him a background of

fundamentals on which he can erect a sound structure in later years. This is not being done with respect to inheritance in diseases. Although much is being published on this subject by those interested, it is not universally read, because the practitioner has not the necessary basic knowledge to enable him to grasp even the significance of many of the terms which are used.

It is true that at present there does not seem to be a great financial return from this particular study, and that therefore there will be need for the creation of endowed chairs in medical genetics, whereby research workers in this important field can not only teach medical students but can continue their investigations. As the profession and the public become alive to the possibilities, and as the latter learn to seek medical aid before the disease has started rather than after its onset, the physician will get his returns in the field of prevention rather than cure. Physicians are interested, and are becoming progressively more so, as they are learning more of the subject. One enlightened medical health officer, who is on a national Board of Examiners for medical licensure, regularly questions the candidates upon heredity in disease. He is keenly alive as to its public health aspects. The more general inclusion of such questions in State Board examinations would stimulate an interest in the subject. The matter of including in the Royal Society of Medicine in England a section which shall be devoted solely to reports of hereditary diseases is being advocated. The medical atmosphere is working toward the saturation point; there now must soon come a precipitation into an

organized course of medical genetics designed to teach the student what is known of inheritance in disease.

PROPOSED CONTENTS OF COURSE

The following is a brief outline of a proposed course in Medical Genetics to be offered to students in their final year of medicine. The course would consist of thirty-six hours of lectures as a minimum and, depending upon the available clinical material in the hospital at the time, a certain amount of practical work. There would be much leeway here in the line the practical work would follow, just as there is variation in the choice of material for medical or surgical clinics.

The time table would be as follows:

- 2 hours. The fundamental concepts of inheritance, with special reference to the problems as met with in man.
- 2 hours. Heredity in endocrine diseases.
- 3 hours. Blood and blood vascular diseases in relation to heredity.
- 1 hour. Vasomotor and trophic disturbances.
- 1 hour. Genito-urinary disease.
- 2 hours. Digestive diseases and hereditary diseases of the spleen.
- 2 hours. Anomalies of metabolism.
- 3 hours. Eye diseases.
- 2 hours. Skin diseases.
- 2 hours. Skeletal diseases and malformations.
- 5 hours. Diseases of the nervous and neuro-muscular systems.
- 4 hours. Mental diseases.
- 3 hours. Tumors, benign and malignant.
- 1 hour. Miscellaneous conditions.

- 1 hour. Monstrosities and multiple births.
- 1 hour. Correct method of compiling family histories.
- 1 hour. Preventive and public health aspects of the problem.

Below are listed some of the conditions which would be discussed under each of the above headings.

1. Fundamental concepts of inheritance. Direct, indirect, sex-linked inheritance. Variations in mode of inheritance of disease in different families. Age factors in inherited disease.
2. Endocrine disturbances. Goiter, simple, exophthalmic; myxedema. Diabetes insipidus. Obesity. Adiposa dolorosa, Laurence-Biedl syndrome. Addison's disease. Diabetes mellitus. Miscellaneous endocrinopathies.
3. Blood and blood vascular system. Inheritance in blood groups, from medico-legal standpoint. Hemorrhagic diatheses including hemophilia, purpura hemorrhagica, and the great unclassified groups belonging to neither of the above. Telangiectasia, hemoptysis, hematuria, hematemesis. Pernicious anemia. Achylia gastrica. Sick cell anemia. Polycythemia. Leukemia. Congenital defects of the heart. Hypertension, apoplexy, hypotension, angina pectoris. Varicose veins.
4. Vasomotor and trophic disorders. Urticaria, epidermolysis bullosa, angio-neurotic edema, chronic edema, Raynaud's disease.
5. Genito-urinary diseases. Albuminuria of idiopathic origin. Polycystic kidneys. Bladder atony. Polymastia. Hermaphroditism. Hypospadias. Phimosis. Varicocele. Cryptorchidism, imperforate hymen, etc.
6. Digestive system. Liver and spleen. Gastric ulcer. Absent or malformed parts of digestive tract, such as salivary glands, atresia of esophagus, hypertrophic pyloric stenosis, imperforate anus, situs inversus, etc. Icterus neonatorum, acholuric jaundice, Gaucher's disease, cirrhosis of the liver, etc.
7. Anomalies of metabolism. Ortho-glycemic glycosuria, gout, alkaptonuria, cystinuria, pentosuria, steatorrhea, porphyrinuria, urobilinuria.
8. Eye diseases. Ptosis, ophthalmoplegia externa and interna, lagophthalmus, cryptophthalmus, blue sclerae, pterygium, megalocornea, microcornea, keratocornea, cornea plana, embryotoxon, corneal opacities not due to syphilis or tuberculosis, microphthalmus, anophthalmus, hydrophthalmus, glaucoma, defective or absent iris, cataract, ectopia lentis, color blindness, day blindness, night blindness, retinitis pigmentosa, amaurotic family idiocy, juvenile and adult forms of heredo-degeneration of the macula, glioma retinae, optic atrophy, hypermetropia, myopia, nystagmus, astigmatism, strabismus.
9. Skin diseases. Anomalies of hair color, distribution, and absence of hair, teeth, sweat glands, etc. Dystrophies of the nails, of the teeth, of the skin. Tumors of the skin. Albinism, etc.
10. Skeletal malformations. The deformities of hand and foot, as polydactyly, brachydactyly, syndactyly, monodactyly, ankylosis, club foot and hand, contracture of fingers, fragilitas ossium, multiple cartilaginous exostoses, cranio-cleidodysostosis, oxycephaly, acrocephaly, achondroplasia, dwarfism, absent radii, cervical ribs, congenital dislocation of the hip, and numerous dystrophies of the bones and joints, cleft palate, hare lip.
11. Diseases of the nervous and neuromuscular systems. Progressive central muscular atrophy, Wernig-Hoffmann atrophy of infants, amyotrophic lateral sclerosis, hereditary spastic paraplegia, peroneal atrophy, Friedreich's ataxia, Marie's cerebellar ataxia, multiple sclerosis, extra-cortical axial aplasia, cerebral diplegia, Schiller's encephalitis, word blindness.

aphasia, paralysis agitans, hepato-lenticular degeneration, athetosis, facial paralysis, syringomyelia, myoclonus, periodic paralysis, tremor, neurofibromatosis, miscellaneous nervous disorders. Muscular diseases: muscular dystrophies, amyotonia congenita, myotonia atrophica, myotonia congenita.

12. Mental diseases.

Migraine, epilepsy, Huntington's chorea, microcephaly, mongoloid imbecility, macular degeneration, dementia praecox, manic depressive states, feeble-mindedness, etc.

13. Tumors.

All types of tumors of all organs, with evidence from the statistical standpoint as to the frequency of any given tumor in the population at large, and its significance in more than one member of the family.

14. Miscellaneous conditions.

Deaf mutism. Status lymphaticus. Allergic diseases. Hernia. Left handedness.

15. Multiple births. Monstrosities.

Twinning, anencephaly, spina bifida, hydrocephalus, hydropic kidney, etc.

16. Correct method of compiling family history with practical work.

In conclusion, let me again emphasize that, as we eliminate through our admirable public health organizations those diseases which are transmissible from person to person by means of infectious organisms and by filterable viruses, we are raising the percentage of the population who will fall victim to hereditary diseases. Some of these diseases may be of great importance only to the persons immediately concerned, and by the institution of preventive methods, these persons may have their lives still further prolonged for usefulness in the community. Many of the diseases, however, have a very direct public health aspect, since they are transmissible by germ plasm if not by organisms; they are of great economic importance to the public, since their victims require public aid in the maintenance of institutions, doctors and nurses to look after them. The only way to meet both problems is to have a medical profession trained and alert in the matter of human inheritance.

Editorial

THE USE OF LABORATORY PROCEDURES IN THE PRACTICE OF MEDICINE

Medicine has for centuries been so closely interwoven with the social relations of mankind that it is, and always must remain, a social function or profession; therefore, whatever affects people economically will also affect medicine. That such a statement is true, is amply borne out by the present depression of medical activities, and at the same time by the numerous studies and publications which are being constantly brought forward, all dealing more or less with the subject of the excessive cost of medical care, and all seeking a solution of a much unsettled and debatable problem.

Contemporary medicine has not yet been tempered with a proper degree of humility, and professional credulity—a benign form of unintentional dishonesty—has become a disease of very serious public menace. Specialists expound views, describe methods and allege cures, based far too much on impressions rather than facts. Specialism has made almost preposterous growth, and short-cuts to diagnosis, and extravagant methods of therapy are widely exploited. Credulity, as thus utilized in both diagnosis and treatment, has in part been responsible for some of the distrust in the medical profession among the rank and file of laymen, for admitted dissatis-

faction within the ranks of the profession itself, and it has at least a bearing upon this problem of the so-called cost of medical care—a current subject of such heated discussion.

Excessive or improper reliance upon laboratory procedures has been conspicuous, particularly within recent years, and is believed by many to be one potent factor in the production of some of the practitioner's contemporary difficulties. Such a condition, if admitted, need not continue to exist.

There are perhaps four main ^{categories} of laboratory methods or ^{techniques} _{tion}

(a) Those of pure research

(b) Those of presumed but unproved value. These have a legitimate field; their number will always be large and their diligent study is to be encouraged. From all of them a few will survive, as a result of accredited merit. Probably their clinical application should be studiously restricted to hospitals and teaching institutions, until their relative value, intrinsic sources of error or utter uselessness have been decisively demonstrated.

The alert practitioner and consulting internist should be informed about these two groups, though not actively concerned in their clinical application until their final status has been established.

(c) Those of established value, but of a complexity which puts their application beyond the range of the average individual, by reason of ex-

pensive equipment, the technic required or the time involved, or the infrequency of their need. In such a group one might mention basal metabolic rates, the Wassermann reaction, intricate clinical bacteriological studies, blood chemistry determinations, roentgen-rays and electrocardiographic tracings. Fortunately, the utilization of tests in this group is necessary in but a relatively limited number of cases. To use them intelligently, but three things are needed: An understanding of the physiological or pathological basis for the test; an unwillingness to interpret the results except in correlation with all the clinical data, critically judged by sound common sense; and first-hand information as to the methods used and care exercised in the laboratory in which the tests are made.

(d) Finally, those tests of long-tried and proved worth, simple, requiring a minimum amount of laboratory apparatus and a small expenditure of time, each capable of yielding diagnostic information which every physician should be able to interpret correctly. In this group might be included the simpler studies of the blood, urine, feces, gastric contents, spinal fluid and sputum. Years of teaching and observation corroborate Peabody's remarks that "in spite of the great contributions which the laboratory has made to clinical medicine, there has been surprisingly little change in the character or number of the technical methods that are essential to good practice. In spite of the extraordinary influence the laboratory has had on the development of medical science, as well as of medical education, there is

as yet no cause for the physician to feel that he cannot keep up with the requirements of the best modern methods." The physician who cannot or does not judiciously utilize laboratory procedures is deficient in his clinical practice, and adds needlessly to the economic problems of the profession.

It would be utterly futile to argue against either the value or the usefulness of many laboratory methods which have been evolved in recent years. Yet in the excessive reliance upon, or in the unsound, non-discriminating use of, or the incompetent interpretation of laboratory tests, one can find a tremendous menace to modern medical efficiency; and so long as dogmatic reliance upon laboratory methods keeps reflective thinking and systematic observation subservient, poor clinical practice will continue.

The particular level to which an individual rises in terms of intellectual development depends upon the degree and consistency with which he exercises his many "mental muscles". The power of observation, the process of reasoning, the instincts of curiosity and wonder, keenness in special sense perception, are but so many intellectual muscles. They develop and expand by use; they wither and atrophy through disuse. Mental muscular development can be attained only through industry. This does not begin and end with the conscientious performance of the daily task. For those in the medical profession it means relentless study, inspired by a perennial, insistent demand for the solution of perplexities. Sustained mental development of this sort can be secured only by the exercise of hon-

esty, not merely in our dealings but in our thinking. Too few of us take the pains to study the origin of our cherished convictions. We are incredibly heedless in the formation of beliefs, and become filled with an illicit passion for them when any one proposes to rob us of their companionship. The

world today needs sadly more of the intellectual freedom of the Greeks, the self-detachment and self-abnegating vigor of criticism so strikingly illustrated in the honest "know-nothingism" of Socrates.

SYDNEY R. MILLER.

Reviews

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith, Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital. *Volume III: Practice of Medicine.* Associate Editor: HAROLD M. MARVIN, B.A., M.D., Assistant Clinical Professor of Medicine, Yale University School of Medicine. lii + 1400 pages, 44 illustrations. 1933. D. Appleton and Company, New York and London. Price, \$10.00.

In the June, 1932, issue of the ANNALS, Volumes I and II of *The Practitioner's Library of Medicine and Surgery* were reviewed. These dealt, respectively, with Anatomy and Physiology as Applied to Practical Medicine and with The Technic of Physical and Laboratory Examination in Clinical Medicine. The entire set will consist of twelve volumes of which the last will be a composite index. Each volume is indexed separately as well. The present volume (III, *Practice of Medicine*) presents the material ordinarily covered in the standard textbook on internal medicine, with the exception of diseases of the nervous system. As compared to the texts of but a few years ago the changing emphasis on various diseases is apparent. Thus we find chapters devoted to Tularemia, Undulant Fever, Rat-Bite Fever, Psittacosis, Benzol Poisoning, and Agranulocytosis. Also there is added emphasis upon occupational hazards and industrial medicine in general.

To this volume there are 30 contributors. To list them all, with the subjects upon which they have written, would exceed the limits of this review. J. Burns Amberson provided the section on Tuberculosis; Alvin L. Barach, on Diseases of the Nose, Larynx, Bronchi, Lungs and Pleura; Arthur L. Bloomfield, on Streptococcal Infections; H. L. Bockus, on Diseases of the Liver, Gall-Bladder, Bile Ducts and Pancreas; Oswald E. Deeney, on Leprosy; W. W. Duke, on Allergic Diseases; Raphael Isaacs, on The Anemias, Polycythemia, Leukemia, Lymphoblastoma, Agranulocytosis and Hemorrhagic Diseases; H. M. Marvin, on Diseases of the Heart and Diseases of the Blood Vascular System, and John H. Musser, on Typhoid Fever, Colon-Paratyphoid Infection, Tularemia, Influenza, Whooping Cough, Diphtheria, Tetanus, Anthrax and Glanders; to mention but a few of the authors.

As is inevitable with so many different authors, there is a marked difference in scale in the presentation of various topics. Throughout there is an evident desire to present the essentials. Some authors have done more; a few have, perhaps, fallen short of that goal. Generally speaking, those conditions which may be considered of minor importance have received even less attention than their position would seem to indicate. The short chapter of but one and one-half pages on Trichinosis may be taken as an example. As a matter of book-making it is to be questioned whether the many very short chapters should

been grouped; Chapter XXI, *Micrococcus Catarrhalis* Infections, has but 12 lines of text.

With but very few exceptions, the sections of this book are well written discussions of disease states. No one book can give exhaustive treatment to the constantly expanding field of internal medicine. The expert in a particular disease may find that in this book the extremely detailed information which has come to seem essential to him is lacking. Yet to the student and practitioner this volume can be fully recommended as presenting in a clear and attractive manner the necessary material for an understanding of the basic principles of the Practice of Medicine.

C. V. W.

Children's Tonsils In or Out. By ALBERT D. KAISER, M.D., xvii, plus 307 pages. J. B. Lippincott Company, Philadelphia, 1932. Price, \$5.00.

This book, written as such a work should be by a pediatrician, is an interesting study and discussion of the relationship between pathologic processes in the tonsils and adenoids and general and local disease. It discusses the effects of tonsillectomy and adenoidectomy in prevention and treatment of about twenty different pathological states, not only those known to be associated with diseased tonsils, as rheumatic fever, glomerulonephritis, sore throat, etc., but also such indefinite and elusive conditions as malnutrition, anorexia, and mental retardation.

Most of the statistics are based on a ten-year study of 4,400 school children in Rochester, New York, the removal of whose tonsils was recommended. Half of the children of this group were operated upon; the other half, for various reasons, were not. The children were followed for ten years after tonsillectomy had been done or recommended, and the incidence of disease in both groups studied. For example, of the tonsillectomized group, 36 per cent had repeated attacks of sore throat before operation, and only 10 per cent had such attacks in the ten year period after operation. In the non-tonsillectomized group the figures showed a 41 per cent incidence of repeated sore throats before operation was recom-

mended and a 35 per cent incidence in the following ten year period. The figures for the incidence of rheumatic fever are interesting; 2.3 per cent in the tonsillectomized group and 3.5 per cent in the controls, during the ten year period after operation was either recommended or done.

The lack of comparison of the observed statistics to those reported by other authors is noticeable. One also notes the absence of observation of the efficacy of tonsillectomy in preventing subacute bacterial endocarditis.

The section on anatomy, physiology and bacteriology of the tonsils is written by K. E. Birkhaug; that on the tonsils in communicable disease by W. L. Bradford; that on asthma and hay fever by S. S. Bullen. The indications for tonsillectomy in diabetes mellitus are discussed by G. B. F. Gibbs. A chapter on the surgical consideration of incomplete tonsillectomy and the significance of lymphoid hyperplasia is written by E. S. Ingersoll.

Children's Tonsils In or Out is interesting, easy to read, and the graphic charts can be analyzed at a glance. It is certain to be useful in spreading clearer understanding of the positive and the doubtful indications for tonsillectomy, and will certainly prevent many needless operations.

T. N. C.

Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System. By HARVEY CUSHING, 234 pages with 99 illustrations. Charles C. Thomas, Springfield, Ill., 1932. Price, \$5.00.

The papers included in this volume had been delivered as lectures before prominent medical societies and published in current scientific periodicals. They "have been brought together for the convenience of those whom the general theme may interest". They include:

I. Neurohypophyseal Mechanisms from a Clinical Standpoint, the basis of the Lister Memorial Lecture, delivered at the Royal College of Surgeons of England, July 9, 1930.

II. Posterior-Pituitary Hormone and Parasympathetic Apparatus, basis of the William Henry Welch Lecture at Mount Sinai Hospital, New York, April 30, 1931.

III. The Basophil Adenomas of the Pituitary Body and their Clinical Manifestations (Pituitary Basophilism), basis of the Alpha Omega Alpha Lecture given at Yale University, February 24, 1932.

IV. Peptic Ulcer and the Interbrain, basis of the Balfour Lecture, given on Lister Day at the University of Toronto, April 8, 1931.

In these papers the author deals in a charming way with a fascinating field that is of fundamental importance to the general physician as well as to the neurologist, the endocrinologist, and the neurologic surgeon. The author has devoted much of his professional life and talents to the elucidation of the subjects herein discussed, and if there is a fault to be found in the discussion, perhaps it lies in the possibility that the smoothness of his attractive style may make this difficult, intricate, and controversial field seem too easy and too readily comprehensible. Some of his interpretations have been questioned by equally prominent workers in the same field and the author himself says in the preface, "Dealing as they do with somewhat novel topics—or at least with old topics from a renovated standpoint—it is quite probable that many of the interpretations are based on false premises and that even those which appear to be more securely grounded will not stand the test of time. This will make little difference, provided the papers help to draw attention to the long neglected interpeduncular region of the brain, unquestionably of fundamental importance to each of us, whatever may be his special field of medical work." Such situations are, of course, unavoidable in a rapidly changing scientific field.

Certainly there is no one better fitted by his own work and interests to present this subject to the profession, and the reader's

pleasure will be enhanced by the literary excellence of the presentation and by the evidences of the author's scholarship.

T. P. S.

Asthma, Hay Fever and Related Disorders. A Guide for Patients. By SAMUEL M. FEINBERG, M.D., F.A.C.P., 124 pages, illustrated. Lea and Febiger, Philadelphia, 1933. Price, \$1.50.

The conventional approach, used by the authors of most textbooks upon this subject, is used here. Starting with a historical review of the subject and working through such topics as complications, etiological agents, method of history taking, skin testing procedures, treatment, general care and advice, the book closes with a brief discussion of conditions which are less surely members of the specific sensitivity group of phenomena, although generally conceded as belonging in it, in some instances at least.

The author has limited his appeal strictly to the needs of the lay patient, avoiding the pitfalls inherent in any attempt to reach both patient and physician. Because of this, a dogmatic approach which materially aids in simplifying the subject for the uninitiated is permissible and is used with reasonable restraint.

The subject matter is handled in a clear and satisfactory manner, with the exception of an occasional tortuosity of expression that is not vital.

Certain phases of modern medicine are dependent upon concepts and considerations differing widely from those applying to medicine as a whole; it would seem that this was peculiarly true of manifestations of specific sensitivity. For that reason, a book of this sort should be of definite value as an aid in the clinical management of these cases.

H. M. B.

College News Notes

The executive office of the American College of Physicians will greatly appreciate information concerning any Fellows of the College who will be in Switzerland in August of the coming summer, at the time of the meeting of the International Goiter Conference in Berne.

Acknowledgement is made of the following gifts to the College Library of publications by members:

Dr. H. Sheridan Baketel (Fellow), Jersey City, N. J.—1 reprint;

Dr. W. R. Brooksher (Fellow), Fort Smith, Ark.—1 reprint;

Dr. Ralph O. Clock (Fellow), New York, N. Y.—2 reprints;

Dr. Ronald L. Hamilton (Fellow), Sayre, Pa.—1 reprint;

Dr. Maurice Kovnat (Associate), New Brighton, N. Y.—3 reprints;

Dr. Howard E. Marchbanks (Fellow), Pittsburg, Kansas—2 reprints;

Dr. Sydney Nussbaum (Associate), Brooklyn, N. Y.—8 reprints.

Dr. Harold F. Machlan (Fellow), was recently officially transferred from the Veterans Administration Hospital at Indianapolis to the hospital associated with the Veterans Administration Home, Dayton, Ohio.

Dr. S. A. Slater (Fellow), Worthington, Minn., was recently reappointed a member of the Minnesota Medical Executive Board. Dr. Slater is Superintendent of the Southwestern Minnesota Sanatorium, a member of the Board of Directors of the Minnesota Public Health Association and, during January of this year, was elected President of the Sioux Valley Medical Society.

Dr. David Riesman (Fellow), Philadelphia, Pa., has been elected Professor of

the History of Medicine in the University of Pennsylvania to fill a newly established chair in this subject.

Dr. P. W. Rowland (Fellow), Professor of Pharmacology, University of Mississippi, was elected President-Elect for 1934-35 of the Mid-South Post Graduate Medical Assembly, at its recent meeting (49th) at Memphis, Tenn.

Dr. John A. Kolmer (Fellow), and Dr. Henry L. Bockus (Fellow), both of Philadelphia, Pa., under the auspices of the Medical Society of New Jersey, in coöperation with Rutgers University, recently delivered lectures on "Pneumonia Therapy" and "Diseases of the Liver", respectively, in connection with a series of graduate lectures for members of the Union County (N.J.) Medical Society.

Dr. John V. Smith (Fellow), Perth Amboy, N. J., has been appointed a member of the State Board of Institutions and Agencies.

Dr. Adolph Sachs (Fellow), Omaha, Nebr., has been elected Vice President of the newly organized Omaha Mid-West Clinical Society, the membership of which is limited to one hundred physicians.

Dr. Harlow Brooks (Fellow), New York City, has been named as an Adviser of the recently organized New York Institute of Clinical Oral Pathology. The initial membership is made up of one hundred physicians and dentists. It is announced that the activities of the organization will be extended over the country.

Dr. Karl E. Kassowitz (Fellow), Milwaukee, Wis., was recently elected President of the Milwaukee Pediatric Society.

Dr. Walter L. Bierring (Fellow), Des Moines, Iowa, was reelected Secretary of the Federation of State Medical Boards of the United States at the Chicago meeting, February 13-14, 1933.

Dr. William D. Cutter (Fellow), Chicago, Ill., who is Secretary of the Council on Medical Education and Hospitals of the American Medical Association, was appointed Managing Editor of the *Federation Bulletin*.

Dr. Henry A. Rafsky (Fellow), has been appointed Consulting Gastro-Enterologist to

the Rockaway Beach Hospital, New York City.

Dr. Charles H. McEnerney (Associate), Washington, D. C., was recently reelected Secretary-Treasurer of the American Society for the Study of Arthritis; also Dr. McEnerney has been appointed as Consultant in Arthritis to the Providence Hospital, Washington, D.C.

Dr. David W. Kramer (Associate), Philadelphia, Pa., was recently promoted to Assistant Professor of Medicine at the Jefferson Medical College of Philadelphia.

ABSTRACT OF THE MINUTES OF THE MEETINGS OF THE BOARD OF REGENTS

Montreal, Canada
February 6-10, 1933

First Meeting, February 5

The Board of Regents of the American College of Physicians was presided over by Dr. F. M. Pottenger, President, Monrovia, Calif. The following members were present: Drs. Francis M. Pottenger, Maurice C. Pincoffs, George Morris Piersol, William D. Stroud, William Gerry Morgan, Walter L. Bierring, John H. Musser, O. H. Perry Pepper, James H. Means, James Alex. Miller, David P. Barr, Arthur R. Elliott, James B. Herrick, Clement R. Jones, Noble Wiley Jones, and W. Blair Stewart.

Dr. Carl V. Weller, retiring Editor of the *ANNALS OF INTERNAL MEDICINE*, was present on invitation. The Executive Secretary, E. R. Loveland, acted as Secretary of the meeting.

Abstracted Minutes of the previous meeting of the Board of Regents held at the College Headquarters, Philadelphia, November 13, 1932, were read and approved.

As incompleting business from the preceding meeting of the Board, the following resolutions were presented by Dr. William Gerry Morgan, Secretary-General.

DR. ELMER HENDRICKS FUNK

In an organization such as the American College of Physicians, with a restricted membership, the withdrawal of

a single member by resignation or death is always an occasion for regret. In the death of Dr. Elmer Hendricks Funk the College sustains a loss greater than the mere withdrawal of one of its most influential members.

He was born in the City of Philadelphia and there he grew up and was educated, having received his medical education at Jefferson Medical College, from which he graduated with honor in 1908. He served there as resident physician, chief resident physician, medical director, and medical director and physician in charge in the department for diseases of the chest. He also served as resident physician in the Philadelphia Hospital for Contagious Disease and the Whitehaven Sanitarium for Tuberculosis. In all of these important posts he left behind him an enviable record for the highest type of medical efficiency as well as for his unflinching gentle courtesy and fair dealing.

Dr. Funk was blessed with the rare gift of winning the confidence, respect, and affection of those great leaders in medicine with whom he was fortunate enough to be thrown during the formative years of his professional career. These happy contacts contributed no little to the rapid strides which he early made in scientific medicine.

He had a prodigious capacity for work so that his days were filled with intensive study "investigation, research, teaching, writing, lecturing, work for organized medicine and civic philan-

thropy," all of the most dependable type and of the highest scientific value.

He contributed to many standard works and published in 1930 his volume entitled "The Diseases of the Respiratory Tract." He was recognized as an authority on the subject of tuberculosis.

On April 1, 1923, Dr. Funk was elected a Fellow of the American College of Physicians. At the San Francisco meeting in April 1932, he was unanimously elected Treasurer. His death occurred on May 13, 1932, before he had been able to undertake the arduous duties attached to that office. His death at the age of 46 prematurely cut short a career of great promise and has robbed the medical profession and the public of one of the most gifted men of his generation.

WHEREAS, Divine Providence has seen fit to remove from our midst through sudden and untimely death Dr. Elmer Hendricks Funk, who although among the younger Fellows was yet an earnest and energetic member and a physician of great promise; therefore be it

RESOLVED, That in his death the profession and the American College of Physicians has sustained an irreparable loss; and be it further

RESOLVED, That we extend to his bereaved family our deepest sympathy and send them a copy of these resolutions, and be it further

RESOLVED, That these resolutions be entered upon our records.

DR. JOHN ALDEN LICHTY

The name of John Alden Lichty is indelibly linked with the history of the development and progress of the American College of Physicians. Perhaps no single member has contributed more toward raising the College to its present enviable place among the outstanding medical organizations of the world. His untiring zeal and devotion to the best interests of the College is one of the bright pages in that history.

Dr. Lichty was born in Meyersdale, Pennsylvania, February 26, 1866. He graduated from Mount Union College, from which he received several degrees, and from the University of Pennsylvania School of Medicine in 1893, and from the University of Berlin in 1896. He occupied many important posts, among which may be mentioned Associate Professor of Medicine, University of Pittsburgh School of Medicine; visiting physician, Mercy Hospital, Pittsburgh; visiting physician, Columbia Hospital, Pittsburgh; consulting physician, Presbyterian Hospital, Pitts-

burgh; Superintendent of Clifton Springs Sanitarium, which position he occupied at the time of his death. He was a member of many of the leading medical organizations of this country, and was past president of the American Gastro-Enterological Association. Dr. Lichty was a prolific writer, having published many splendid articles upon a variety of medical subjects. He contributed to several standard textbooks.

Dr. Lichty was elected a Fellow of the American College of Physicians on December 29, 1916. For many years he was a member of the Board of Regents, and for two years was third Vice-President. Of his many signal contributions to the College, perhaps the most notable was his organization of the Credentials Committee, of which he was the first Chairman, and on which he served with distinction.

In the death of Dr. Lichty on May 2, 1932, the College sustained an irreparable loss. Perhaps no single activity in Dr. Lichty's life was nearer to his heart and thoughts than were the affairs of the College.

WHEREAS, Almighty God in his wisdom has taken from among us Dr. John Alden Lichty, one of our oldest and most devoted members, who for more than forty years was a distinguished clinician; therefore be it

RESOLVED, That we enter upon our records this minute of our lasting regret at his passing, and our sincere appreciation of his long life of devotion to the best interests of his profession and of this College; and be it further

RESOLVED, That a copy of this report, preamble, and resolutions be sent to his bereaved family.

DR. CHARLES G. LUCAS

With the passing of Dr. Charles G. Lucas to his eternal rest July 7, 1932, the American College of Physicians has been deprived not only of one of its loyal members, but also of one of its strong, dependable guiding influences throughout nearly all of the years since it came into being.

Born in Cincinnati in 1868, Dr. Lucas received his education both premedical and medical in the institutions of Louisville, Kentucky. It was there that he carried on the practice of his profession. And during all those years was a member of the faculty of the Medical Department of the University of Louisville, in which in 1915 he was made Chief of the Department of Gastro-Enterology, a position he held until his death.

Dr. Lucas was a member of many of the leading medical organizations of the United States, among which was the American Gastro-Enterological Association, of which he was President in 1926; and the American College of Physicians, and served on the Board of Regents 1922-1923 and 1925-1928.

Few men in our profession enjoyed as wide a circle of devoted friends as did this outstanding physician. He will be keenly missed throughout the land wherever medical men foregather.

WHEREAS, By the inscrutable decree of Divine Providence the American College of Physicians has lost in the death of Dr. Charles G. Lucas one of its most esteemed members, who for many years took a leading and active part in the conduct of its affairs, as well as being an outstanding member of his profession; therefore be it

RESOLVED, That we enter upon our records this minute of our lasting regret at his passing and our sincere appreciation of his long life of devotion to the best interests of his profession and of this College; and be it further

RESOLVED, That a copy of this report, preamble, and resolutions be sent to his bereaved family.

Dr. Morgan further reported upon deaths of members during the past year, amounting to twenty-five Fellows and seven Associates; sixteen of these had been previously reported to the Board of Regents, the following being the additional list:

Fellows:

F. T. Billings, Pittsburgh, Pa., January 5, 1933.

Edward Bates Block, Atlanta, Ga., October 25, 1932.

Henry Daspit, New Orleans, La., December 19, 1932.

Gayfree Ellison, Norman, Okla., December 22, 1932.

William Engelbach, Springfield, Ill., November 22, 1932.

Edward Louis Heintz, Chicago, Ill., December 7, 1932.

Frank H. Pratten, London, Ont., December 10, 1932.

William Sydney Thayer, Baltimore, Md., December 10, 1932.

Carl Victor Vischer, Philadelphia, Pa., November 15, 1932.

Associates:

Alfred Henry, Indianapolis, Ind., December 12, 1932.

Fenton Benedict Turck, New York, N. Y., November 16, 1932.

Upon motion regularly moved, seconded and carried, it was

RESOLVED, that the report of the Secretary-General be accepted.

Dr. William D. Stroud, Treasurer, reported, in connection with incompleting business from the previous meeting, that in accordance with resolutions adopted by the Board of Regents, new bank accounts had been opened in the Royal Bank of Canada, Montreal, and the Provident Trust Company, Philadelphia; and that the securities belonging to the College had been transferred from Pittsburgh to the Girard Trust Company, Philadelphia.

The report of the Treasurer was received and placed on file.

In the absence of Dr. Sydney R. Miller, Chairman of the Committee on Constitution and By-Laws, the Executive Secretary presented his report. In accordance with instructions of the Board of Regents, the Committee on Constitution and By-Laws had published the recommended amendments to the By-Laws in the January Issue of the ANNALS OF INTERNAL MEDICINE. The amendments provide for:

(1) A consolidation of the Committee on Credentials, so that in the future there will be but one Committee for both Fellowship and Associateship. This Committee to be comprised of three members from the Board of Regents and three members from the Board of Governors;

(2) To provide that the Editor of the ANNALS OF INTERNAL MEDICINE shall be an ex-officio member of the Board of Regents.

The amendments were to be submitted at the General Business Meeting at Montreal on February 9. Upon motion regularly adopted, it was

RESOLVED, that the amendments, as presented by the Committee on Constitution and By-Laws, be approved.

Dr. George Morris Piersol, Chairman of the Committee on Credentials, presented the

following candidates, whose election to Fellowship was recommended:

Charles William Crankshaw, Consultant and Medical Advisor, Staff of the Medical Department-General, Prudential Life Insurance Company, Newark, N. J.;

Luis Manuel De Bayle, Nicaraguan Minister to the United States, Washington, D. C.;

Charles Austin Doan, Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio;

John B. Doyle, former Assistant Professor of Neurology, Graduate School of Medicine, University of Minnesota, and Neurologist to St. Vincent's Hospital, Hospital of the Good Samaritan and Queen of Angels Hospital, Los Angeles, Calif.;

Everett Colgate Jessup, Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, Roslyn, N. Y.;

Josephine Carrier Lawney, Dean and Professor of Medicine, Woman's Christian Medical College, Shanghai, China;

Malcolm Thomas MacEachern, Director of Hospital Activities, American College of Surgeons, Chicago, Ill.;

Thomas Turlay Mackie, F.R.C.P. & S., D.N.B., Instructor in Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.;

Harry A. Pattison, Director, Potts Memorial Hospital, Livingston, N. Y.;

George Alfred Skinner, Colonel, M.C., U. S. Army, Omaha, Nebr.;

Willard Burr Soper, Associate Professor of Medicine, Yale University School of Medicine; Medical Director, William Wirt Winchester Hospital, New Haven, Conn.;

Nathan Bristol Van Etten, Member, Committee on the Costs of Medical Care; Medical Director, Morrisania Hospital, New York, N. Y.

For Advancement from Associateship to Fellowship:

Arnold S. Anderson, St. Paul, Minn.

Ralph Lee Fisher, Detroit, Mich.

Michael Robert Haley, Dayton, Ohio.

Arthur Fisher Heyl, New Rochelle, N. Y.

John Francis Kenny, Pawtucket, R. I.

Erwin Curtis Miller, Worcester, Mass.

Frank B. Morrissey, St. Paul, Minn.

Rudolph Virchow Powell, St. Louis, Mo.

Benjamin Bruce Souster, St. Paul, Minn.

Edwin Chester Swift, Jacksonville, Fla.

Henry Hubert Turner, Oklahoma City, Okla.

J. Russell Twiss, New York, N. Y.

Upon motion by Dr. O. H. Perry Pepper, seconded by Dr. Arthur R. Elliott, and regularly carried, it was

RESOLVED, that the above list of physicians be and herewith is elected to Fellowship in the American College of Physicians.

Dr. Carl V. Weller, retiring Editor of the ANNALS OF INTERNAL MEDICINE, presented a report, reviewing his experience as Editor of the ANNALS and making suggestions and recommendations concerning the journal in the future. Among his comments, he mentioned the fact that 393 separate papers passed through the editorial office in the last nineteen months, indicating that there is an increased volume of material from which to select articles for publication in the journal, and, therefore, an added opportunity to improve the quality of the material selected for publication. In the past, it had been Dr. Weller's practice to devote approximately fifty per cent of the available space in the ANNALS to the papers delivered at the Clinical Sessions and fifty per cent to the papers selected from those submitted from at large for publication. In addition, it has been his aim to have the final article in each number represent the history of medicine, or ethical, or cultural aspects of medicine. He suggested the desirability of occasionally giving a comprehensive survey or review of some subject such as has not been done in the past. In regard to the size of the ANNALS, he recommended the present size of approximately one hundred and fifty pages per issue as desirable, but with effort expended upon the improvement of the quality of the journal; and he further recommended that the personality and individuality which the journal has achieved be maintained, and that changes in format and composition of material should be gradually

changed, if such changes are thought desirable. Dr. Weller has considered the *ANNALS OF INTERNAL MEDICINE* chiefly as a medium for postgraduate education in internal medicine. Its purpose was not to broadcast the more complicated pieces of work in experimental medicine, but to serve as the medium for postgraduate education to the more than three thousand subscribers scattered over the country.

On motion by Dr. Means, seconded and regularly carried, it was

RESOLVED, that the Board of Regents of the American College of Physicians extend to Dr. Carl V. Weller a vote of thanks for his very able conduct of the *ANNALS OF INTERNAL MEDICINE* since the death of Dr. Warthin.

The following resignations, after being individually considered, were by resolution accepted:

Fellows:

William P. Buffum, Providence, R. I.
A. H. W. Caulfeild, Toronto, Ont.
Clyde L. Cummer, Cleveland, Ohio.
Linton Gerdine, Athens, Ga.
H. Brooker Mills, Philadelphia, Pa.
A. W. Moody, Winnipeg, Man.
Walter B. Mount, Montclair, N. J.
Warren T. Vaughan, Richmond, Va.

Associates:

Edwin H. McIlvain, Philadelphia, Pa.
Henry J. Walton, Baltimore, Md.

Action on the resignation of the following was by resolution deferred:

Fellows:

I. Hope Alexander, Pittsburgh, Pa.
Thomas B. Fitcher, Baltimore, Md.
Edward Livingston Hunt, New York, N. Y.

Associates:

R. W. Baer, Frederick, Md.
James W. Bruce, Louisville, Ky.
J. W. Earl Ellenberger, Wilksburg, Pa.
James J. Gable, Norman, Okla.
Charles A. Howland, Schenectady, N. Y.
Thaddeus Walker, Grosse Pointe, Mich.
Everett E. Watson, Salem, Va.

President Pottenger suggested that there were two matters that should receive some

thought and be referred to the proper Committees. The first one concerns the question of the admission of new members to Associateship. The By-Laws provide that a candidate may be presented for Associateship after he has been graduated but three years, but this does not give the candidate sufficient time, in many cases, to be known by our Fellows in his locality, nor does it assure the College of the fact that he will remain in the field of internal medicine.

Dr. Pottenger, after some discussion by the members of the Board, suggested that possibly the Regent or the Governor in a given district might have a Committee of five or six Fellows appointed before whom candidates would come for a personal interview before their credentials would be referred to the Committee on Credentials.

The other matter President Pottenger wished to present was the suggestion of a change in our method for electing Life Members. He wished to refer to the Finance Committee for their consideration some plan by which members, so to speak, might underwrite their dues for the balance of their lives, and thus become Life Members. For instance, the maximum Life Membership Fee might be, as at present, \$400.00, in addition to a Fellow's initiation fee. However, from the period of forty-five years of age to sixty-five years of age (when a member's dues may be waived), the member would need to pay only an amount equal to his dues for the intervening years. For instance, if a man is fifty years of age, he would pay his dues for fifteen years and become a Life Member, which would entitle him to active membership not only until sixty-five years of age, but for his entire lifetime. Many Fellows should be attracted to this plan of Life Membership who have not been attracted to the previous plan, requiring a total payment of \$500.00. Dr. Pottenger further referred to findings established by skilled actuaries which show conclusively that life membership could be carried successfully and to the benefit of the organization initiating this plan.

Adjournment.

Second Meeting, February 7

The following members of the Board of Regents were present: Drs. F. M. Pottenger, George Morris Piersol, Maurice C. Pincoffs, Noble Wiley Jones, William D. Stroud, William Gerry Morgan, Walter L. Bierring, George E. Brown, John H. Musser, O. H. Perry Pepper, James S. McLester, Jonathan C. Meakins, James H. Means, James Alex. Miller, David P. Barr, Arthur R. Elliott, James B. Herrick, Clement R. Jones and Mr. E. R. Loveland, Executive Secretary.

Minutes of the previous meeting were abstracted and approved as read.

Dr. William Gerry Morgan, Secretary-General, presented several cases concerning fees and dues of individual members. Individual action is recorded in the official Minutes of the College. The following principles, however, were maintained: (1) the regular rules concerning annual dues as printed in the folder of the College should be maintained. This refers to the matter of \$10.00 being the minimum to which the dues of full-time medical teachers and full-time employees of the State may be reduced; (2) former members who were dropped because of delinquency may be reinstated by the Board of Regents subject to the payment of all their delinquent dues; (3) the Board of Regents may waive partially, or fully, the dues of members who are physically incapacitated, but the waiver of said dues shall be made from year to year, subject to the recovery of the member and his again entering practice; (4) members shall not be required to pay dues after they have reached the age of sixty-five years, but the responsibility for notifying the Executive Offices shall be that of the member.

Upon motion regularly moved, seconded and carried, it was

RESOLVED, that the College donate to the John Crerar Library of Chicago the *ANNALS OF INTERNAL MEDICINE*, Volume VI, Nos. 1 to 6, inclusive.

Upon motion by Dr. McLester, seconded and regularly carried, it was

RESOLVED, that the Board of Regents approve of the action taken and the letters submitted by Drs. Pottenger and Morgan in connection with adding the influence of

the American College of Physicians to the Medical Library Association for a reduction in the prices of German medical journals to subscribers in this country.

On behalf of the Chairman of the Board of Governors, Dr. W. Blair Stewart, who was absent, the Executive Secretary presented the following list of 112 candidates whom the Board of Governors had recommended to the Board of Regents for election to Associateship:

Edward Lee Alexander, Newport News, Va.

Francis William Baldwin, New York, N. Y.

Paul M. Bassel, Temple, Texas.

George C. Beach, Jr., Fort Sam Houston, Texas.

Orpheus J. Bizzozero, Waterbury, Conn.

LeRoy Walton Black, Rutherford, N. J.

James Lewis Blanton, Fairmont, W. Va.

Frank Runcorn Borden, Randolph Field, Texas.

James Albert Bradley, New Orleans, La.

Raymond W. Bradshaw, Oberlin, Ohio.

Timothy F. Brewer, Hartford, Conn.

Paul Brindley, Galveston, Texas.

Boyd Franklin Brown, Huntington, W. Va.

Harold F. Brown, Buffalo, N. Y.

Clyde Windom Brunson, Brooklyn, N. Y.

D. Grant Campbell, Montreal, Que.

Guy Walter Carlson, Appleton, Wis.

Douglas Gordon Chapman, Richmond, Va.

Charles Walter Clarke, New York, N. Y.

Thomas J. Coogan, Chicago, Ill.

Henry Charles Crossfield, East Orange, N. J.

Grover Cleveland Dale, Goldsboro, N. C.

Ward Darley, Jr., Denver, Colo.

Frank Lowell Dunn, Omaha, Nebr.

Edgar Durbin, Denver, Colo.

Philips J. Edson, Pasadena, Calif.

Ray Elledge, Hammond, Ind.

William White Falkener, Newport News, Va.

Ralph Manos Fellows, Galveston, Texas.

Clement Coleman Fenton, Morgantown, W. Va.

Carl Herman Gellenthien, Valmora, N. M.

Mark Gerstle, Jr., San Francisco, Calif.

George Albert Gray, Abilene, Texas.

Percival Allen Gray, Jr., Santa Barbara, Calif.
 Edward Alfred Greco, Portland, Maine.
 David S. Greenspun, Bridgeport, Conn.
 Joseph Hajek, New York, N. Y.
 Ronda Horton Hardin, Banners Elk, N.C.
 Robert Ammiel Hare, Santa Barbara, Calif.
 Benedict Richard Harris, Hamden, Conn.
 Edward Hagerman Hashinger, Kansas City, Mo.
 Michael Gerard Healy, Randolph Field, Texas.
 Joseph Emmet Hirsh, Birmingham, Ala.
 Roy Herbert Holmes, Muskegon, Mich.
 D. Waldo Holt, Greensboro, N. C.
 Arthur Hartt Jackson, Washington, Conn.
 Guy Carleton Jarratt, Vicksburg, Miss.
 Clarence Emory Johnson, Long Beach, Calif.
 George Stephen Johnson, Denver, Colo.
 Harry Gardner Johnson, Buffalo, N. Y.
 Ernest L. Kiesel, Scranton, Pa.
 John Glenwood Knauer, Washington, D.C.
 Vincent W. Koch, Janesville, Wis.
 Rudolph A. Kocher, Carmel, Calif.
 Elmer Elgin Kottke, Des Moines, Iowa.
 Manfred Kraemer, Newark, N. J.
 Roderick Alexander Macaulay, Springfield, Mass.
 Frank Rowe Maddison, Tacoma, Wash.
 Bernard Abraham Manace, Corvallis, Ore.
 Frank Raymond Mazzola, Jamaica, N. Y.
 David William McKechnie, Montreal, Que.
 Bernardine Thomas McMahon, Loomis, N. Y.
 Joseph Marion Messick, Rochester, Minn.
 Albert John Michels, East Liverpool, Ohio
 Ida J. Mintzer, Jamaica, N. Y.
 Edward Winfield Miskall, East Liverpool, Ohio.
 Morris Eli Missal, Rochester, N. Y.
 Daniel Murrah Molloy, Guatemala City, Guatemala
 Allen Hoyt Moore, Doylestown, Pa.
 Anita Mary Mühl, San Diego, Calif.
 Frederick William Mulsow, Cedar Rapids, Iowa.
 Jerome A. Murphy, Buffalo, N. Y.
 Frederick W. Niehaus, Omaha, Nebr.
 Edward Sterling Nichol, Miami, Fla.

Joseph Frederick Painton, Buffalo, N. Y.
 George Washington Parson, Texarkana, Texas.
 John Ryer Poppen, Washington, D. C.
 Ernest Boring Porter, Coronado, Calif.
 Harold Walter Potter, Newport News, Va.
 Harry Hansell Preston, Hot Springs, Ark.
 Robert McNair Purdie, Houston, Texas.
 Warren Wilson Quillian, Coral Gables, Miami, Fla.
 Jesse Dean Riley, State Sanitorium, Ark.
 James O. Ritchey, Indianapolis, Ind.
 Samuel Frederick Rosen, Savannah, Ga.
 Max Harold Ruby, Waterbury, Conn.
 Edwin Philip Russell, Rome, N. Y.
 Robert Burns Sanderson, Crown Point, Ind.
 Victor Ewald Schulze, Rochester, Minn.
 Francis J. Scully, Hot Springs, Ark.
 Harold Nathan Segall, Montreal, Que.
 Laurence Fox Segar, Detroit, Mich.
 Henry Kirven Speed, Sayre, Okla.
 George Black Stericker, Springfield, Ill.
 Landon Elwood Stubbs, Newport News, Va.
 George Courtney Stucky, Lansing, Mich.
 George B. Topmoeller, Cincinnati, Ohio.
 Clarence Johnson Tidmarsh, Montreal, Que.
 Neville Thompson Ussher, Santa Barbara, Calif.
 Samuel A. Vogel, Buffalo, N. Y.
 James C. Walsh, Watertown, N. Y.
 Harold M. Walton, Loma Linda, Calif.
 James Harold Watkins, Montgomery, Ala.
 Francis Charles Weber, Newark, N. J.
 Emil Weiss, Chicago, Ill.
 William Graham Weston, Vicksburg, Miss.
 James H. Wheeler, Henderson, N. C.
 Joseph Wiener, Asbury Park, N. J.
 Dwight Locke Wilbur, Rochester, Minn.
 John Woodworth Wilce, Columbus, Ohio.
 Ruth Walker Wilson, Beaver, Pa.
 Burton L. Zohman, Brooklyn, N. Y.
 The entire list was examined individually by members of the Board of Regents, after which the following resolution was adopted:
 RESOLVED, that the above list of candidates shall be and are herewith elected to Associateship in the American College of Physicians.

The Executive Secretary presented mimeographed copies of the financial report of the College for 1932. The accounts of the College had been audited by an accountant and his detailed report was attached. Estimated income and expenditures for 1933 and suggested budgets were also presented. The reports were not discussed, but put in the hands of the Regents for examination and later analysis.

The Executive Secretary presented a list of forty-four names of members who were two or more years delinquent in their dues, and who, according to the By-Laws, are subject to being dropped from membership. The list had been presented to the Board of Governors and some of them expressed a desire to have a few weeks to go over it in a final effort to influence desirable members to retain their memberships and to make provision for the payment of their dues. It was pointed out that out of a total membership of more than twenty-eight hundred, this was a comparatively small list of delinquent members. On motion by Dr. Pepper, seconded and regularly carried, it was

RESOLVED, that the list of members delinquent for two or more years be referred to the individual Governors for the districts in which such delinquents reside, and if after a period of a month thereafter such delinquent members do not make arrangements for the payment of their dues, they may be dropped automatically from the rolls of the College.

Dr. James Alex. Miller, in the absence of Dr. Charles G. Jennings, Chairman, presented the report of the Committee on Public Relations as follows:

REPORT OF COMMITTEE ON PUBLIC RELATIONS

The final report of the Committee on the Costs of Medical Care is entitled: "Medical Care for the American People."

It is the twenty-eighth publication of a series representing an extensive and intensive effort to collect the factual data concerning numerous problems involved. These studies were made over a period of five years, after the expenditure of an extraordinary amount of thought, effort, and money.

The facts presented are of immense

importance to the country as a whole and the medical profession in particular. They deserve the most careful study and consideration.

The detailed information is contained in the twenty-seven interim reports previously published, and only a brief summary is included in the final report. The main emphasis of the final report is placed upon certain definite recommendations proposed by the Committee as the basis for a plan of reorganization of medical practice, so as to meet the social and economic defects of the existing system brought out by the factual data.

These recommendations are in the form of separate majority and minority reports with a few members of the Committee declining to assent to either report.

The widespread discussion which has followed the publication of the final report is centered upon the recommendations suggested. This is most unfortunate as it has overshadowed the great value and significance of the studies upon which these recommendations are presumably based.

It is the opinion of your Committee that the publication of definite recommendations was premature and unjustified by the facts presented. A careful analysis of the text of the reports shows that the recommendations are really only tentative suggestions for future consideration and careful experimentation, and in our opinion should have been offered as such.

It is also our belief that the actual factual data contained in the various reports are of such value that they deserve most careful study on the part of the medical profession. These facts reveal a situation which calls for consideration and action leading to modification of existing medical practice, and in any such modification the medical profession should take a leading part.

It would be very unfortunate if prejudice caused by differences of opinion concerning the recommendations should belittle the value of the facts themselves. It would be still more unfortunate if either prejudice or inaction should deprive the medical profession of its rightful position of leadership in any program for remedying existing inequalities or injustices in the operation of the practice of preventive and curative medicine.

Our Committee, therefore, recommends that the individual Fellows of the American College of Physicians be urged to study the facts presented in the report of the Committee on the

Costs of Medical Care, uninfluenced by the acrimonious discussion which has been raised by the publication of the various recommendations, and we also recommend that the organized representatives of the medical profession in each community be urged to consider these problems in the light of their varying local needs and conditions, for it is our belief that by this method the enlightened leadership of the medical profession can point the way to improvements of great value, both to the public and to the medical profession itself.

In commenting upon the report, Dr. Miller said that the Regents might desire to have this report read at the General Business Meeting of the College and to have it published in the *ANNALS OF INTERNAL MEDICINE*. On motion recorded and regularly carried, it was

RESOLVED, that the Board of Regents of the American College of Physicians hereby approves the report of the Committee on Public Relations and directs that said report be printed in the *ANNALS OF INTERNAL MEDICINE*.

Dr. James B. Herrick re-presented the cordial invitation of the City of Chicago, as extended at the November meeting of the Board of Regents, for the College to meet in Chicago during 1934.

Adjournment.

Third Meeting, February 10

With Dr. George Morris Piersol presiding, as the new President, the meeting was attended by the following Regents: Drs. George Morris Piersol, Francis M. Pottenger, Maurice C. Pincoffs, William D. Stroud, William Gerry Morgan, Walter L. Bierring, John H. Musser, O. H. Perry Pepper, James S. McLester, Jonathan C. Meakins, James H. Means, James Alex. Miller, David P. Barr, Clement R. Jones, W. Blair Stewart, Luther F. Warren and Mr. E. R. Loveland, Executive Secretary.

Dr. Piersol introduced Dr. Luther F. Warren, of Brooklyn, newly elected member of the Board. The Executive Secretary acted as Secretary of the meeting.

By resolution, the Minutes of the previous meeting of the Board of Regents were dispensed with. The President called upon

the Executive Secretary to present his report on the finances of the College, which follows. Mr. Loveland analyzed for the Board the comparative cost of conducting the last four Clinical Sessions and other details of the financial statements. He said in part: "When I submitted estimates of Income and Expenditures for 1932, one year ago, I estimated that the surplus for the year would be \$9,970.00. The year's operation discloses a surplus of \$9,623.08, or a difference of only \$356.92. The total cash income for 1932 was \$75,785.31, which is mentioned merely to apprise the Board of the volume of College business transacted. During the year 1932, \$9,623.08 was added to the General Fund, making a total of \$64,810.97; \$975.00 was added to the Endowment Fund, making a total of \$53,375.00. The combined funds now amount to \$118,185.97.

" Increased expenditures for 1932 were occasioned by a far more expensive meeting, due to its being held in San Francisco and due to the awarding of the John Phillips Memorial Prize for the first time. While the *ANNALS OF INTERNAL MEDICINE* showed a deficit of \$1,266.13 on Volume V, the journal showed a surplus for the calendar year of 1932 of \$196.27. This improvement in the financial publication of the journal is due chiefly to the following: (a) a reduction in printing costs; (b) an increase, even under the present financial conditions, in the advertising income; (c) efficient and helpful coöperation of the Editor. A comparison of the advertising income in the past four years follows:

1929—\$2,263.46

1930— 3,543.49

1931— 3,929.26

1932— 4,536.84

"Your Executive Secretary's office has been conducted as conservatively as possible, consistent with the business interests of the College. A reduction was secured in the rental of the College Headquarters, the extra budget for the Treasurer's office has been eliminated since the Treasury was transferred to Philadelphia, and one of the more highly paid secretarial assistants in the Executive Secretary's office was dispensed with on June 1, 1932. In the last

instance we may have erred, because the burden of work thrown upon the other assistants and the Executive Secretary has been so great in the preparation for this Session that all have frequently had to work late at night, Saturday afternoons and Sundays.

"During the year 1932, \$4,077.82 has been invested, or reinvested, additionally in securities, bringing the total holdings up to \$65,574.55. The cash balance on December 31, 1932, amounted to \$48,285.55, of which \$18,311.79 was on deposit in closed banks. During 1932, \$8,892.54 was repaid by closed banks. The balance is carried on the books at its face value, due to the fact that the ex-Treasurer, Dr. Clement R. Jones, has assured the Board of Regents in the past that these balances will be paid in full.

"The budgets submitted for 1933 have been prepared as conservatively as possible by me. In view of the reduced income from Fellowship initiation fees occasioned by changed admission requirements, the reduction of Fellowship dues from \$20.00 to \$15.00 and of Associateship dues from \$15.00 to \$12.00, the reduction of Clinical Session guest fees from \$15.00 to \$12.00, the estimated surplus for 1933 is \$5,142.50. The budgets provide for such economies as: a continued reduction in the office staff of the Executive Secretary, a reduction of 10 per cent in the Executive Secretary's salary, a reduction of 10 per cent in the Editor's salary, a reduction of \$20.00 per month in the rental of the College headquarters, and all other savings that can reasonably be made."

Dr. Clement R. Jones, Chairman of the Finance Committee for 1932-1933, presented his report, recommending the following: (1) that remaining College accounts in closed banks in Pittsburgh be assigned by him as the former Treasurer to the "American College of Physicians"; (2) that the Board of Regents authorize the purchase of \$5,000 in U. S. Bonds in addition to the \$1,000 authorized at the meeting on November 13, for permanent investment; (3) the Committee recommends to the Board of Regents the reduction in the cost of Life Membership to \$300.00, plus the initiation

fee, up to the age of forty-five years. After forty-five years of age, the Life Membership fee shall be equivalent to the initiation fee plus the amount of dues from that age to sixty-five years of age. All Fellows now paying for Life Membership on the installment plan may come under this reduced amount; (4) the Committee recommends to the Board of Regents that the Editor's compensation shall be restored to \$2,500 a year; (5) the Committee recommends to the Board of Regents the approval of the auditor's report and the financial accounts for the year 1932.

Dr. Pottenger commented upon the recommendation of the Committee in regard to Life Membership. He said that up to forty-five years of age, a member will pay his regular \$300.00, plus the initiation fee; at forty-six, he would deduct from the \$300.00 one year's dues; at forty-seven, two years' dues, and so on. He stated that the plan gives the member an opportunity of paying his Life Membership while he is productive, and expressed the hope that a great many members would desire to pay their memberships in full during the time their income is greatest, thus avoiding the burden the dues might be in later life. On the other hand, fees so paid will go into the permanent fund of the College.

Upon motion, seconded and regularly carried, the report of the Committee on Finance was accepted and the recommendations adopted.

Dr. W. Blair Stewart, a member of the Committee on Insignia, requested the Executive Secretary, Mr. Loveland, to read the report of the Chairman, Major Edgar Erskine Hume, who could not be present. The report was discussed freely and its recommendations were adopted in the following form:

"(a) A cross of the shape of that of the Key of the College, approximately three inches in height, of green velvet or cloth to be worn at the option of the member on the right side of the academic gown to indicate Fellowship in the College;

"(b) A similar cross of gold braid or cloth of gold would indicate Mastership in the College.

"The use of cloth insignia of this type is in accordance with historical

precedent, and some of the gowns worn by continental University officials and others have such badges to indicate rank or special marks of merit. This plan has the advantage of being quite inexpensive, and as it is optional there should be no complaint by members of having to purchase insignia. On the other hand, if used by Fellows and others on commencement and other occasions, it will be a dignified means of indicating membership in this College. Moreover, if it is decided at some future time to adopt some special gown or hood, there would be practically no expense to making the change."

Upon motion made, seconded and regularly carried, it was

RESOLVED, that the Editor of the ANNALS OF INTERNAL MEDICINE and the Executive Secretary of the College, in conference with the Committee on Publications, be given the authority to change the printer of the ANNALS if they feel it desirable between now and the next meeting of the Board of Regents.

Dr. Stewart, Chairman of the Board of Governors, reported briefly on the work of the Board of Governors during the year, and of their meetings in Montreal. His report indicated that there has been a great deal of activity among the Governors in their individual communities and all are thoroughly interested in the work of the College. He reported to the Board of Regents that he, as Chairman of the Board of Governors, and by authority delegated to him by the Board, had appointed as members of the Committee on Credentials Dr. Egerton L. Crispin, Los Angeles, Calif., for a period of three years; Dr. Chas. H. Cocke, Asheville, N. C., for a period of two years; and Dr. Ernest B. Bradley, Lexington, Ky., for a period of one year.

The first matter under new business was the election of the Secretary-General and the Treasurer for the ensuing year. Dr. Clement R. Jones nominated the present incumbents, namely, William Gerry Morgan for Secretary-General and William D. Stroud for Treasurer, which nominations were regularly seconded. Dr. Musser moved the nominations be closed, said motion being seconded and carried. The Secretary, Mr.

Loveland, was instructed to cast the ballot, and declared Dr. Morgan and Dr. Stroud regularly elected as Secretary-General and Treasurer, respectively, for the ensuing year.

In accordance with the provisions of the Constitution and By-Laws, the following Executive Committee for 1933-1934 was elected:

George Morris Piersol, Philadelphia, Pa.,
Chairman

Jonathan C. Meakins, Montreal, Que.

William Gerry Morgan, Washington, D.C.

William D. Stroud, Philadelphia, Pa.

Walter L. Bierring, Des Moines, Iowa

James H. Means, Boston, Mass.

James Alex. Miller, New York, N. Y.

Maurice C. Pincoffs, Baltimore, Md.

Francis M. Pottenger, Monrovia, Calif.

Upon motion by Dr. Pincoffs, seconded and regularly carried, it was

RESOLVED, that the American College of Physicians accept the invitation of the City of Chicago to hold its 1934 Clinical Session there.

Upon motion by Dr. Pincoffs, seconded and regularly carried, it was

RESOLVED, that Dr. James B. Herrick be appointed General Chairman of the 1934 Clinical Session, and that the exact date of the meeting and the headquarters be left to the General Chairman and the Executive Secretary.

President Piersol, in accordance with authority included in a resolution adopted by the Board of Regents on November 13, 1932, appointed the following standing Committee on Finance:

Charles F. Martin, Montreal, Que.,
Chairman. (3 years)

James Alex. Miller, New York, N. Y.
(2 years)

James S. McLester, Birmingham, Ala. (1
year)

President Piersol reported that there were certain other Committee appointments to be made, but with the approval of the Board, he would prefer deferring the appointments for some of these vacancies, until he had had an opportunity to consider the requirements more fully.

Adjournment.

ABSTRACT OF MINUTES OF THE MEETINGS OF THE
BOARD OF GOVERNORS

Montreal, Canada

February 6-10, 1933

First Meeting, February 6

A regular meeting of the Board of Governors was held on the above date, and presided over by Dr. W. Blair Stewart, Chairman, with the following additional members present: Drs. Oliver C. Melson, Edward L. Tuohy, A. Comingo Griffith, Charles Hartwell Cocke, Clarence H. Beecher, J. Morrison Hutcheson, D. Sclater Lewis, Lewis B. Flinn, Edwin W. Gehring, Luther F. Warren, A. B. Brower, Charles T. Stone, Egerton L. Crispin, Henry F. Stoll, Samuel E. Munson, Thomas Tallman Holt, Adolph Sachs, Allen A. Jones, Leander A. Riely, Edward J. G. Beardsley, John O. Manier, Jabez Elliott, Charles Edward Riggs and Mr. E. R. Loveland, Executive Secretary.

The Executive Secretary, E. R. Loveland, acted as Secretary of the meeting, and read abstracted Minutes of the last meeting of the Board, which were approved as read.

He commented upon the application of the new rules for the admission of members, and asked Governors to investigate candidates fully and to write accordingly to the College Headquarters concerning each candidate. Dr. Stewart then reviewed the time requirements for Associates, namely, that a physician to be presented for Associateship must be a graduate of three years' standing, must not be younger than twenty-six years of age, and that after he has been elected an Associate, he becomes eligible for proposal for advancement to Fellowship at the end of three years, and must qualify for Fellowship within five years. At the end of that time, except by specific action of the Board of Regents, he will be automatically dropped from the rolls of the College. There followed some discussion as to whether or not twenty-six years of age is not too young, and whether three years after graduation is not too short a time for a man to be considered for Associateship. It was directly inferred that members of the Board of Governors should have this in mind when recommending younger men for election to Associateship,

and that possibly only exceptional candidates should be considered at this early age.

Dr. Stewart also pointed out the effect of the new amendment to the By-Laws, which would consolidate the Committee on Credentials for Fellowship and the Committee on Credentials for Associateship; the new Committee to be composed of three members from each Board.

The Chairman further commented upon the list of elections to Fellowship by the Board of Regents, explaining that those elected directly to Fellowship were men of great prominence in various parts of the country, and outstanding men in the medical profession. They are physicians of mature years in professional work. All of their cases have been thoroughly investigated, and every one of them unanimously approved for election to Fellowship. The College is not interested in number of members, but in men of outstanding ability.

Chairman Stewart commented upon the clinical program prepared for the Montreal meeting, and expressed the opinion that the College owed the General Chairman, Dr. Meakins, a debt of gratitude for his work and that of his Committees. The President, Dr. Pottenger, also had prepared an outstanding program for the general sessions, and his work deserved the highest commendation. Dr. Stewart then expressed his appreciation and thanks to the Executive Secretary, Mr. Loveland, for his work. He said the Executive Secretary should not be considered an employee of the College, but as a man who has had the interests of the College at heart from the very moment he took his position, and whose work deserves outstanding recognition by all.

Chairman Stewart introduced President-Elect George Morris Piersol, who spoke briefly of the work of the Committee on Credentials, of which he had been Chairman for many years, and of the new Consolidated Committee which is planned to further facilitate and improve the work of selecting members in the future. He commended

the work of the various Governors and pointed out that they could be of even greater assistance by being firm in applying the requirements of the College to new candidates and by not forwarding to the College Headquarters any proposals but those which in their opinion merit election. He pointed out that the cost of investigating candidates varies from five to twelve dollars, depending upon the size of the community from which the proposal comes. This cost is made up chiefly from clerical service and postage, because letters or inquiry cards are addressed to every Fellow of the College in the community, or city, from which the proposal arises. Dr. Piersol further stated that present economic conditions have caused an increasing number of members to present their resignations, although the number coming into the College is much smaller than the average of other organizations. It is an appropriate function of the Governors to investigate such resignations, and not only to report upon them to the Executive Secretary, but to make an effort to retain desirable men in the College. Dr. Piersol then took occasion to say that the members were deeply indebted to the Executive Secretary for his work and for his coöperation in cutting down the expenses of the College.

At the request of Chairman Stewart, the Executive Secretary read a letter, expressing his regret at being unable to attend the meeting and conveying his regards to the Board, from Dr. Edward O. Otis, Governor for the State of New Hampshire, and dean of the Governors, being the oldest member.

Chairman Stewart introduced President Pottenger, who had just entered the meeting room. Dr. Pottenger spoke briefly of the importance of the Board of Governors in connection with their work in building the membership of the College and the selection of candidates. The Board of Governors should be an increasingly active body; it stands between the Board of Regents and the College membership; it fulfills the essential requirement of having a thoroughly active member representing every State and every Province. Dr. Pottenger reemphasized the remarks made by President-Elect

Piersol in regard to the application of the standards of admission.

Dr. Allen A. Jones, Chairman of the Committee on Credentials for Associateship, presented a list of sixty-four candidates whose credentials had been carefully reviewed by the College and deemed adequate for election to Associateship at a meeting of the Committee on November 13, 1932, at the College Headquarters, and another list of forty-eight candidates whose credentials had been reviewed on February 5 at Montreal.

Upon motion by Dr. Crispin, seconded by Dr. Griffith and regularly carried, it was

RESOLVED, that the complete list of 112 candidates be approved by the Board of Governors and recommended to the Board of Regents for election to Associateship. (The complete list appears in the Minutes of the Board of Regents as published on another page.)

The Executive Secretary presented a list of forty-four delinquent members of two or more years standing who were subject to being dropped from the rolls of the College. He asked individual members of the Board of Governors to look over the list for their particular districts and to be prepared to make recommendations in the course of the next month. In the meantime, the Board of Regents would be asked to delay action on the list, pending recommendations of the Board of Governors.

The Executive Secretary reported the death of twenty-five Fellows and seven Associates since the San Francisco Clinical Session.

The Executive Secretary reported upon action of the Board of Regents in connection with accepting and deferring various resignations. He distributed mimeographed copies of the financial reports of the College for 1932, and analyzed important features thereof.

On motion by Dr. Cocke, seconded and regularly carried, it was

RESOLVED, that it be the sense of the Board of Governors to express their appreciation to the Executive Secretary for his splendid work in this time of stress and for his efforts in maintaining such an excellent financial status as shown by the reports.

The Chairman opened the meeting for an open forum for discussion or comment by members of the Board.

Dr. Edward L. Tuohy, Governor for Minnesota, made the following inquiries: to what degree are the Associates in Minnesota qualifying for Fellowship under the three-year rule; does the College encourage membership among physicians engaged in border-line specialties, such as Pediatrics, Neurology and Roentgenology; should not the College concentrate more upon Internal Medicine; has the Board of Regents given any more attention to the matter of regional conferences with fewer annual meetings of the wider scope.

The Executive Secretary was asked to answer the first question. He pointed out that Associates who had been elected previous to 1929 were under no obligation to qualify for Fellowship, but those elected during 1929 and thereafter are required to qualify for Fellowship within five years. At the end of three years after election, an Associate is notified by the Executive Secretary that he is now eligible to be considered for Fellowship, and that he is expected to present the qualifications for Fellowship within two more years. In Minnesota, the majority of the Associates elected in 1929 have qualified for Fellowship. For the Committee on Credentials, Dr. Allen A. Jones expressed the opinion that Dr. Tuohy's second point was well taken, and that it should have further consideration. The Committee on Credentials have considered men engaged in the border-line specialties of Pediatrics, Neurology and Roentgenology eligible, provided they present proper credentials. It was pointed out that the General Chairman of each Clinical Session attempts to provide something in the Program for the men interested in the affiliated specialties, as well as Internal Medicine.

It was stated that there was a consensus of opinion that the present type of Annual Clinical Sessions would have greater value than regional conferences, but that the leading city would be alternated from one section of the country to another, in order that members in each region would have opportunities to attend the meetings periodically,

if they could not travel longer distances every year.

Dr. Crispin opened a discussion concerning the minimum age for Associates, and expressed the opinion that most men at this age are not qualified for Associateship, and that they must be selected with considerable care. Dr. Crispin expressed the opinion that it is incumbent upon the Governors to handle these cases as best they can, but to have in mind the possibility of recommending a higher minimum age than at present provided.

Dr. Samuel E. Munson, Governor for Southern Illinois, made inquiry concerning how Governors shall report unfavorable action by the Committee to the candidates. Dr. Stewart suggested that this must be left to the individual judgment of the Governors. Dr. Cocke, of the Committee on Credentials, stated that approximately fifty per cent of the candidates proposed for Associateship are not immediately elected, but are put on a deferred list for additional data, seasoning, etc.

Adjournment.

Second Meeting, February 9, 12:30 p.m.

The second meeting of the Board of Governors was attended by the following, with Dr. W. Blair Stewart presiding: Drs. Oliver C. Melson, Edward L. Tuohy, A. Comingo Griffith, Charles Hartwell Cocke, J. Morrison Hutcheson, Edwin W. Gehring, Charles T. Stone, Egerton L. Crispin, Henry F. Stoll, Thomas Tallman Holt, Roger I. Lee, Adolph Sachs, Allen A. Jones, Leander A. Riely, Edward J. G. Beardsley, John O. Manier, Jabez Elliott, Charles Edward Riggs and the Executive Secretary, Mr. E. R. Loveland.

The Executive Secretary read an abstract of the Minutes of the previous meeting, which were approved as read.

The Executive Secretary reported that the complete list of candidates recommended by the Board of Governors had been regularly elected to Associateship by the Board of Regents; that the Board of Regents adopted a resolution providing that after the list of delinquent members presented at the previous meeting has been thoroughly

At the direction of Chairman Stewart, the Executive Secretary read the report of the Committee on Public Relations, as approved by the Board of Regents.

Adjournment.

The third meeting of the Board of Governors was held immediately after the General Business Meeting for the purpose of organization of the Board for the new year. The following members were present: Drs. Oliver C. Melson, Edward L. Tuohy, A. Comingo Griffith, W. Blair Stewart, Charles Hartwell Cocke, Clarence H. Beecher, J. Morrison Hutcheson, Edwin W. Gehring, Luther F. Warren, Charles T. Stone, Egerton L. Crispin, Henry F. Stoll, Samuel E. Munson, Thomas Tallman Holt, Roger I. Lee, Adolph Sachs, Allen A. Jones, Leander A. Riely, Edward J. G. Beardsley, Joseph Edward Knighton, Wallace Mason Yater, and Mr. E. R. Loveland, Executive Secretary.

The terms of the Chairman and Vice-Chairman had expired with the Montreal Session, and following the election of new members of the Board of Governors, it be-

Dr. Allen A. Jones, Chairman of the Committee on Credentials for Associateship, presented a list of sixty-four candidates of whom credentials had been carefully reviewed by the College and deemed adequate.

The Executive Secretary list of 112 for the unanimous reelection Board of art as Chairman for the ensuing year. Members of the Board are: Minutes

Nominations for the Vice-Chairman were opened, whereupon Dr. Adolph Sachs placed in nomination the name of Dr. Ernest B. Bradley for reelection.

Upon motion by Dr. Samuel E. Munson seconded and regularly carried, the Chairman of the Board of Governors was instructed to appoint three members to serve on the Committee on Credentials. Chairman Stewart stated he would announce his appointments in the near future.

NOTE: At the end of the Clinical Session, Chairman Stewart announced the appointment of the following members to serve on the Committee on Credentials:

Committee on Credentials:

Egerton L. Crispin, Los Angeles, Calif.
(3 years)

Charles Hartwell Cocke, Asheville, N. C.
(2 years)

Ernest B. Bradley, Lexington, Ky. (1
year)

ABSTRACTED MINUTES—GENERAL BUSINESS MEETING
of the
AMERICAN COLLEGE OF PHYSICIANS

Montreal, Canada

February 9, 1933

The Annual General Business Meeting of the College convened at five o'clock in Windsor Hall, Montreal, with President Francis M. Pottenger presiding.

The Executive Secretary, E. R. Loveland, read an abstract of the Minutes of the previous meeting held in San Francisco, April 7, 1932, which was approved as read. Dr. William Gerry Morgan, Secretary-General, was called upon and read the report of the Committee on Public Relations, approved by the Board of Regents. The answer to the question of the Treasurer, William D. Stroud, Treasurer, presented the following report for the year 1932:

"Upon assuming the office of Treasurer on July 1, 1932, the Treasurer's Office was transferred to the Central Office at 133-135 S. 36th Street, Philadelphia, and the major portion of the secretarial work has been carried on in that office, thus eliminating the extra budget for the Treasurer's Office, entailing a saving to the College of some \$500 during the last half of 1932, and approximately \$1000 a year in the future.

"The total cash income for the year 1932 was \$75,785.31, with operating expenditures, including the unusually heavy expenses of the San Francisco Session, \$66,162.23, leaving a surplus of \$9,623.08, which has been added to the General Fund.

"On December 31, 1932, the Assets of the College were as follows:

General Fund	\$64,810.97
Endowment Fund	53,375.00
Total	\$118,185.97

Of this total, \$65,574.55 is in securities on deposit in the Girard Trust Company of Philadelphia.

"\$18,311.79 is still owing from the three banks in Pittsburgh which went into the hands of receivers in 1930 and 1931. \$8,892.54 has been repaid by these banks during the year 1932. The cash balance on deposit in the Girard Trust Company of Philadelphia, the Provident Trust Company of Philadelphia, the First National Bank of Pittsburgh, and the Royal Bank of Canada was \$48,285.55.

"There have been no defaults in interest by any of our securities during the year 1932, and such interest has totaled \$2,906.43—considerably more than the Phillips Memorial Prize.

"At the November 13, 1932 meeting of the Board of Regents in Philadelphia, the Fellowship yearly dues were reduced from \$20 to \$15, and Associate dues from \$15 to \$12. Considering the times financially, the year 1932 has been definitely successful for the American College of Physicians. For this, much credit is due to the efficiency of the Executive Office and the Executive Secretary.

"Respectfully submitted,
William D. Stroud, M.D.,
Treasurer."

Upon motion seconded and regularly carried, the report of the Treasurer was accepted and placed on file.

The Executive Secretary, E. R. Loveland, presented his annual report. This covered some analysis of the financial report for the year, a report upon the financial side of the publication of the ANNALS OF INTERNAL MEDICINE, the cost of conducting the Annual Clinical Sessions, membership statistics, registration at the Montreal Session and the conduct of the Executive Offices.

Upon motion seconded and regularly carried, the report of the Executive Secretary was accepted and placed on file.

Dr. William Gerry Morgan, Secretary-General, was asked to present the report of the Committee on Constitution and By-Laws. He read the proposed amendments, Article by Article and Section by Section, as published in the January issue of the ANNALS OF INTERNAL MEDICINE.

On motion by Dr. O. H. Perry Pepper, seconded and regularly carried, the amendments were unanimously adopted.

President Pottenger expressed his pleasure at having been the President of the College for the past year and thanked the members of the organization for their coöperation and aid. He especially complimented the efficient organization of the Executive Office.

ces of the College and the organization by Drs. Meakins and Martin of the Montreal Session. He then asked Dr. O. H. Perry Pepper and Dr. W. Blair Stewart to escort the new President, Dr. George Morris Piersol, to the platform.

In introducing Dr. Piersol, Dr. Pottenger said, "It is a happy occasion in one's life when his colleagues elect him to an office such as the Presidency of the American College of Physicians. It is an especially happy occasion at this time because our new President is a man who merits this position, not only because of his professional attainments, but also because of his devoted service to this organization. Dr. Piersol has been one of our hardest-working members. He has been ever thinking of this organization and looking after its interests. I present to you my successor, Dr. Piersol."

Members arose and applauded, after which Dr. Piersol assumed the chair. In his remarks, Dr. Piersol said in part, "Less than a year ago when you honored me by electing me to the head of this organization, I tried to express to you my appreciation and gratitude for that honor. I repeat it now. I am truly grateful to you for having conferred this distinction upon me and for the confidence and trust that you have indicated in me. I am not going to presume on your time now to try to make any sort of a formal address. My opportunity for that, I take it, will come next year. I do want to say, however, that in assuming this office, I do so with full realization of the responsibilities that go with it. I know that it will be a difficult task to live up to the record that has been established by our retiring President and his predecessors. I am hoping that the incoming administration, by reason of its interest and enthusiasm, will be able to accomplish the work in a meritorious way. In order that, during these rather difficult and uncertain times, we can continue to widen the sphere of influence of this organization and maintain its prestige, I earnestly bespeak the coöperation of all of you. Without that, no administration can succeed, but with that help and with the wise advice and counsel of the Board of Regents and the unfailing interest of the Board of Governors, it may be possible dur-

ing this year to have an administration that will terminate its office one year hence in a successful manner. I want to thank you again and tell you how I am counting on all of you for help during the coming year."

Dr. E. J. G. Beardsley, in the absence of the Chairman of the Committee on Nominations, presented the following report:

"A meeting of the Nominating Committee was held at the office of the College in Philadelphia on the evening of November 12, 1932.

"The following nominations were made:

For President-Elect—Dr. J. C. Meakins, Montreal

For First Vice-President—Dr. C. G. Jennings, Detroit

For Second Vice-President—Dr. N. W. Jones, Portland

For Third Vice-President—Dr. J. H. Means, Boston

For Regents:

(Terms expiring 1936)

Dr. W. L. Bierring, Des Moines

Dr. J. H. Musser, New Orleans

Dr. O. H. P. Pepper, Philadelphia

Dr. F. M. Pottenger, Monrovia

Dr. L. F. Warren, Brooklyn

Terms expiring 1934 (to fill vacancy)

Dr. William J. Kerr, San Francisco

The following nominations were made for the Board of Governors:

For the term expiring in 1936:

Dr. Oliver C. Melson, Arkansas

Dr. Hans Lissner, Northern California

Dr. Tom Bentley Throckmorton, Iowa

Dr. Joseph Edward Knighton, Louisiana

Dr. James D. Bruce, Michigan

Dr. Edward L. Tuohy, Minnesota

Dr. A. Comingo Griffith, Missouri

Dr. Edward O. Otis, New Hampshire

Dr. D. Sclater Lewis, Quebec

Dr. W. Blair Stewart, New Jersey

Dr. Charles Hartwell Cocke, North Carolina

Dr. Julius G. Arnson, North Dakota

Dr. Alexander M. Burgess, Rhode Island

Dr. Robert Wilson, Jr., South Carolina

Dr. Clarence H. Beecher, Vermont

Dr. J. Morrison Hutcheson, Virginia

Dr. Frederick Epplen, Washington
 Dr. John N. Simpson, West Virginia

For the term expiring in 1934:

to take Dr. Luther F. Warren's place—
 Dr. Robert Anderson Cooke, New York

For the term expiring in 1935:

(to take the place of Dr. William Gerry
 Morgan, who has become Secretary-
 General—

Dr. Wallace Mason Yater, Washington,
 D. C.

On motion regularly made, seconded and unanimously carried, the report of the Nominating Committee was accepted and the Secretary-General instructed to cast one ballot for the election of all the candidates nominated. The Secretary-General, Dr. Morgan, announced the ballot had been cast, and the nominees elected.

Dr. O. H. Perry Pepper: "Mr. President, it is proper that we should at this meeting pass a vote of thanks to all the various agencies which have contributed to this very remarkably successful meeting. We should include in this vote of thanks the various institutions of Montreal, the various hospitals of the city, the Convention and Tourist Bureau, the press, and other local agencies. We should include especially the General Chairman, Dr. Meakins. Under Dr. Meakins' supervision there have been five or six Committees at work—the Committee on Arrangements, the Committee on Entertainment of Visiting Women (Chairman, Mrs. Meakins), the Committee on Transportation (Chairman, Dr. Kaufman), the Committee on Publicity (Drs. Sutherland and Benoit, joint Chairmen), the Committee on Convocation (Drs. Martin and Harwood, joint Chairmen). To all of these agencies and individuals Mr. President, I move you a rising vote of thanks by the College." The members arose and applauded.

President Piersol asked the President-Elect, Dr. J. C. Meakins, to come to the platform and make a few remarks.

Dr. Meakins: "Mr. President, Masters, Fellows of the American College of Physicians: I wish to express my few words in logical sequence to what has happened this afternoon. I must confess that I read pages

of the ANNALS OF INTERNAL MEDICINE from a scientific point of view more than I do from the news point of view. I have been taught a very sharp lesson. It was just a week ago last night when our Executive Secretary, Mr. Loveland, was dining with me at my home that he informed me I had been nominated for President-Elect, and it had been published in the January issue of the ANNALS. I was, you may quite realize, tremendously surprised that you should have deemed me worthy of such an honor. I am probably one of the younger members of the College. I feel this confidence which you have placed in me imposes the serious obligation to fulfill your expectations. I have a long line of predecessors who have done noble work, and it is difficult to follow such a royal succession. But you may be assured, I will do everything in my power to maintain the dignity, to maintain the scientific and the professional standard of the College, which means so much to the medical profession of North America. I can only thank you sincerely for this honor which you have done me. I accept it with due humility.

"The organization here in Montreal, although there are only a few of us, are all loyal Fellows of the College. It was our desire to make this meeting as great a success as we could. My part in the matter was one as 'general', I suppose, and no general has yet ever won a campaign without brilliant staff officers. The success of this meeting depended upon the staff officers. For them I accept the vote of thanks, and I thank them as well myself. If it had not been for them, the whole organization would have been a miserable failure.

"I cannot let this opportunity pass without expressing my sincere thanks on behalf of myself and the local Committees to Dr. Pottenger for his unfailing kindness, consideration and courtesy to us. Furthermore, I want to make another expression, and that to Mr. Loveland. We were rather ignorant, true, as far as running this campaign was concerned, but his wise guidance, his almost uncanny penetration of our difficulties and what we should do, his clear letters, his unfailing and prompt consideration of us, made this possible.

"I think the American College of Physicians should be particularly thankful that they have such a capable Executive Secretary. It is only those who work with him who can fully appreciate that. I never appreciated it. I thought it was just an ordinary job. It is not; when one gets into the ramifications of it and sees the multitude

of details which he puts before the local Committee, clearly and succinctly, one cannot help but offer him, on my behalf and on behalf of my committee, a very sincere vote of thanks."

All business scheduled to come before the Fellows and Masters of the College having been completed, adjournment followed.

AMERICAN COLLEGE OF PHYSICIANS, INC.
Balance Sheet, December 31, 1932

A S S E T S

CASH:			
In Banks and on Hand	\$30,173.76		
In Banks in Hands of Receivers			
Bank of Pittsburgh	\$7,797.16		
Exchange National Bank, Pittsburgh	3,887.12		
Highland National Bank, Pittsburgh	6,627.51	18,311.79	\$48,485.55
Accounts Receivable			539.11
Investments, as annexed			65,574.55
Accrued Interest on Investments			968.44
Inventory of Keys, Pledges and Frames.....			377.59
Deferred Expenses, 17th Annual Clinical Session (paid in advance).....			2,242.61
Furniture and Equipment	\$3,804.22		
Less allowance for Depreciation	1,604.39	2,199.83	
			<u>\$120,387.68</u>

L I A B I L I T I E S

Deferred Income:			
Advance Collections for Exhibits, 17th Annual Clinical Session	\$1,880.94		
Advance Subscriptions for Volumes 7 and 8, Annals of Internal Medicine	320.77	2,201.71	
			<u>\$118,185.97</u>

F U N D S

Endowment Fund, as annexed	\$53,375.00		
General Fund, as annexed	64,810.97		<u>\$118,185.97</u>

GENERAL FUND, PRINCIPAL
For the year ended December 31, 1932

Balance, December 31, 1931			\$57,166.71
Less:			
Transfer to Endowment Fund of Initiation			
Fees of Life Members paid prior to January 1, 1932.....	\$ 100.00		
Award of John Phillips Memorial Prize and expenses of recipient incident thereto	1,878.82	1,978.82	
			<u>\$55,187.89</u>
Add:			
Net Income for the year, as annexed.....			2,623.03
			<u>\$61,810.97</u>
Balance, December 31, 1932.....			<u>\$61,810.97</u>

ENDOWMENT FUND PRINCIPAL
For the year ended December 31, 1932

Balance, December 31, 1931	\$52,400.00
Life Membership Fees Collected During the Year Ended Dec. 31, 1932.....	975.00
	<hr/>
Balance, December 31, 1932	<u>\$53,375.00</u>

INCOME AND EXPENSES
For the Year ended December 31, 1932

I N C O M E

Annual Dues	\$27,718.00	
Initiation Fees	10,275.00	
Interest on Bank Deposits	381.16	
Income from Endowment Fund	\$2,365.79	
Income from Bonds Owned	540.64	2,906.43
Profit from Sale of Keys, Pledges and Frames... ..		148.54
Collection and Exchange		241.67
Receipts from Annals of Clinical Medicine	6.60	<u>\$41,677.40</u>

E X P E N S E S

Sixteenth Annual Clinical Session

Income:		
Exhibits	\$4,609.73	
Guest Fees	875.00	\$5,484.73
Expenses:		
Salaries	\$4,574.27	
Communications (Postage, Telephone, Etc.)	646.47	
Stationery and Office Supplies	83.55	
Printing	1,927.90	
Traveling Expenses	8,876.00	
Entertainment	286.65	
Advertising	323.00	
Reporting	166.25	
Badges	297.09	
Ladies Committee	98.90	
Publicity	180.83	
Banquet	75.85	
Miscellaneous	557.40	18,094.16
Net Expenses		<u>\$12,609.43</u>

Annals of Internal Medicine

Income:		
Subscriptions		
Volume I	\$ 23.65	
Volume II	6.04	
Volume III	62.25	
Volume IV	44.58	
Volume V	590.17	
Volume VI	17,335.44	
Advertising		
Volume V	2,359.87	
Volume VI	2,176.97	
		<u>\$22,598.97</u>

Expenses:

Salaries	\$5,226.92	
Communications (postage, telephone, etc.)	1,149.64	
Printing	15,840.64	
Traveling Expenses	53.13	
Stationery and Office Supplies.....	3.34	
Miscellaneous	129.03	22,402.70

Net Income \$ 196.27 196.27

Forward.....\$12,609.43 \$41,873.67

"I think the American College of Physicians should be particularly thankful that they have such a capable Executive Secretary. It is only those who work with him who can fully appreciate that. I never appreciated it. I thought it was just an ordinary job. It is not; when one gets into the ramifications of it and sees the multitude

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Less:			
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Fees of Life Members paid prior to January 1, 1932.....	\$ 100.00		
Award of John Phillips Memorial Prize and expenses of recipient incident thereto	1,878.82	1,978.82	
		<u>\$55,187.89</u>	
Add:			
Net Income for the year, as annexed.....		9,623.03	
Balance, December 31, 1932.....		<u>\$64,810.97</u>	

ENDOWMENT FUND PRINCIPAL
For the year ended December 31, 1932

Balance, December 31, 1931	\$52,400.00
Life Membership Fees Collected During the Year Ended Dec. 31, 1932.....	975.00
Balance, December 31, 1932	<u>\$53,375.00</u>

INCOME AND EXPENSES
For the Year ended December 31, 1932

I N C O M E

Annual Dues	\$27,718.00	
Initiation Fees	10,275.00	
Interest on Bank Deposits	381.16	
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E X P E N S E S

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Income:

Exhibits	\$4,609.73	
Guest Fees	875.00	\$5,484.73

Expenses:

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Stationery and Office Supplies	83.55	
Printing	1,927.90	
Traveling Expenses	8,876.00	
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Advertising	323.00	
Reporting	166.25	
Badges	297.09	
Ladies Committee	98.90	
Publicity	180.83	
Banquet	75.85	
Miscellaneous	557.40	18,094.16

Net Expenses \$12,609.43

Annals of Internal Medicine

Income:

Subscriptions	
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II	6.04
III	62.25
IV	44.58
V	590.17
VI	17,335.44

Advertising

Volume V	2,359.87	
VI	2,176.97	
		\$22,598.97

Expenses:

Salaries	\$5,226.92	
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Printing	15,840.64	
Traveling Expenses	53.13	
Stationery and Office Supplies.....	3.34	
Miscellaneous	129.03	22,402.70

Net Income \$ 196.27 196.27

Forward.....\$12,609.43 \$41,873.67

	Forward.....	\$12,609.43	\$41,873.67
<i>Executive Secretary's Office</i>			
Expenses:			
Salaries	\$9,219.31		
Communications (postage, telephone, etc.)	1,085.20		
Stationery and Office Supplies	419.35		
Printing	501.03		
Rent and Maintenance	2,980.84		
Traveling Expenses	2,812.05		
Annual Audit	150.00		
Premium on Surety Bond	20.00		
Miscellaneous	111.24		
		17,299.02	
<i>Treasurer's Office</i>			
Expenses:			
Salaries	\$240.00		
Communications (Postage, Telephone, etc.)	59.50		
Stationery and Office Supplies	4.13		
Printing	2.90		
Traveling Expenses	492.30		
Annual Audit	50.00		
Premium on Surety Bond	153.50		
Fee for Storage of Securities	75.00		
Miscellaneous	10.00	1,087.33	
<i>Annals of Internal Medicine</i>			
Distributed Free to Life Members		144.00	
1932-33 Directory (Cost of Production and			
Distribution of Supplement)		727.19	
Depreciation on Furniture and Equipment		380.42	
Loss on Equipment Traded In		3.20	32,250.59
Net Income for the Year Ended Dec. 31, 1932.....			<u>\$9,623.08</u>

INVESTMENTS December 31, 1932

Par Value	Bonds	Cost
1,000	Borough of Steelton, Pa., Paving, 4½s, Jan. 15, 1933	}\$ 3,071.25
1,000	Borough of Steelton, Pa., Water Improvement, 4½s, Jan. 15, 1933	
1,000	Borough of Steelton, Pa., Fire Apparatus, 4½s, Jan. 15, 1933	
4,000	Canadian National Railway, 4½s, 1956	3,930.00
5,000	Canadian National Railway, 5s, July 1, 1969	} 7,042.50
2,000	Canadian National Railway, 5s, Oct. 1, 1969	
2,000	Canadian National (West Indies) SS. Co., 5s, 1955	2,040.00
2,000	City of Covington, Ky., 4¾s, 1946	2,134.01
2,000	City of Detroit, Mich., Lighting, 4¼s, 1944	2,010.40
2,000	City of Detroit, Mich., Street Ry., 4¼s, 1949	2,025.26
2,000	City of Houston, Texas, School District, 4¾s, 1942	2,077.50
2,000	City of Los Angeles, Calif., Sewage Disposal "B", 5s, 1943.....	2,158.24
1,000	City of Montreal, Canada, 5s, 1956	1,071.30
2,000	City of Newark, N. J., Series 2, 4¼s, 1944	2,075.00
10,000	City of Philadelphia, Pa., 4½s, 1949-79	10,225.00
2,000	City and County of San Francisco, Calif., Fire Protection, 5s, 1941.....	2,137.12
2,000	City of Seattle, Wash., Light & Power, 4¾s, 1957	1,995.00
2,000	City of Toronto, Canada, Local Improvement, deb. 5s, 1936.....	2,020.00
500	Oklahoma Gas & Electric Co., deb. 6s, Series A, 1940	487.50
2,000	Borough of N. Y. Authority, Interstate Bridge Bond, Series B, 4½s, 1952	2,042.20
2,000	Port of New York Authority, Interstate Tunnel, Series E, 4¼s, 1958	2,065.40
2,000	Province of Alberta, Canada, deb. 4½s, 1956	1,896.00
5,000	Province of Ontario, Canada, deb. 4½s, 1933	4,925.79
2,000	Province of Ontario, Canada, deb. 4½s, 1942	2,015.00
1,000	Province of Ontario, Canada, deb. 5s, 1942	1,052.26
2,000	U. S. Treasury, 4s, 1954	1,998.13
3,000	U. S. 4th Liberty Loan, 4¼s, 1938	3,079.60

ANNALS OF INTERNAL MEDICINE

VOLUME VI

MAY, 1933

NUMBER 11

The Clinical Significance of the Systolic Murmur*†

A Study of 1000 Consecutive "Non-Cardiac" Cases

By A. R. FREEMAN, M.D., and SAMUEL A. LEVINE, M.D., F.A.C.P.,
Boston, Massachusetts

INTRODUCTION .

THE significance of the systolic heart murmur has long been a matter of considerable discussion. Not so very long ago, if a heart murmur was heard in a patient, the physician would quickly make a diagnosis of some organic heart condition. If it were systolic in time, and especially if apical in origin, a diagnosis of mitral insufficiency would be made. About fifteen years ago, particularly as a result of the extensive experience with neurocirculatory asthenia, or the so-called soldier's heart during the great war, the pendulum began to swing to the diametrically opposite position. It was found that systolic murmurs were very common in the absence of organic heart disease and gradually the point of view developed that systolic murmurs had no significance whatever. Sir James Mackenzie was frequently

heard to say that it would be better "to throw the stethoscope away". He meant by this that more could be gained by eliciting the symptoms and obtaining an intelligent history of the case, and that auscultation was comparatively valueless. Cabot¹ stated that, "systolic murmurs without other signs of cardiac disease are of no importance as evidence of valve lesions", and that, "a diagnosis of mitral regurgitation without stenosis is never justified". We believe that the truth lies somewhere between these two extreme positions and that, although systolic murmurs are fairly common and often have no importance, frequently they have a definite significance, and a significance that clinically can be ascertained and properly explained. This is in accord with the view recently expressed by Herrick.² On the other hand P. D. White³ stated that "a functional systolic murmur in the pulmonary area is heard in at least 50 per cent of all individuals in the recumbent position". Thayer⁴ found 74 apical

*Received for publication August 29, 1932.

†From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and the Harvard Medical School.

functional systolic murmurs among 218 normal young individuals in the recumbent left lateral position. Lee⁵ found that 70 per cent of normal individuals showed a systolic murmur in the pulmonic or apical regions, in the recumbent position after strong expiration. Yet McCrudden⁶ found a definite decrease in life expectancy in individuals with no other signs of heart disease except an apical systolic murmur.

A study therefore was undertaken to determine how frequently systolic murmurs are present in routine examinations. An attempt was also made to analyze conditions under which systolic murmurs were found. For this purpose 1000 patients were carefully examined with the deliberate aim of detecting heart murmurs. In about half the instances, the patients were examined by both authors. It was quickly found that the observations by one corresponded quite well with those of the other. In order to avoid the large group of heart patients that are present in any general medical clinic, cases in the medical wards were included in the study to only a small extent. As many routine admissions to the surgical service of the Peter Bent Brigham Hospital as we could study were included. Seventy patients in the neighboring infants' and children's hospital were also examined, so that the study might not be confined to adults. Forty-seven students and house officers in the hospital and 120 nurses were included as representative of healthy young adults. In addition, 100 consecutive patients in a tuberculosis sanitarium were added so that we might determine the frequency of

murmurs in a disease which, although wasting, rarely if ever causes changes in the valves of the heart. This is an entirely different approach from that customarily undertaken, when the significance of a systolic murmur in patients coming for cardio-vascular examination is studied. White⁷ in such a study found that 76 per cent of 1050 unselected patients with an apical systolic murmur had organic heart disease.

It is not the purpose of this study to analyze the frequency of systolic murmurs in heart disease or even to try to explain the physical mechanism of these murmurs. It is common knowledge that systolic murmurs are present with valvular and myocardial disease. It is also quite well known that murmurs may be heard although the heart is normal when anemia or changes in metabolism such as occur in hyperthyroidism are present. The confusion in interpretation has not been diminished a great deal by the addition of the terms "organic" and "functional" murmurs. Many a patient has organic heart disease and still has a relative or "functional" mitral systolic murmur. We also believe that many systolic murmurs which are regarded as functional because the patient has no other evidence of heart disease, are, in fact, organic, in the sense that there is a structural change in the valves causing the murmur.

In trying to analyze the significance of systolic murmurs it became evident that the intensity of the murmur was of considerable importance. The situation is in no way different from that found in studying other clinical data. The amount of albumin in the urine is now fairly well standardized by the

terms, S.P.T. (slightest possible trace) ; S.T. (slight trace) ; L.T. (large trace), etc. Likewise the Wassermann reaction is often indicated by the terms of 1 to 4 plus. The same may be said of globulin in the spinal fluid, and of other tests. It is not a difficult matter to train one's ear so that the loudness and duration of the murmur can be indicated by the figures 1 to 6. On this scale, the systolic murmur of grade "1" intensity is the faintest bruit that can be definitely heard. Although quite faint, this sound must have an appreciable duration. It must continue after the first heart sound and well into systole and must not be confused with a prolonged first heart sound that often is present in hyperactive hearts or in thin-chested individuals, merely as a result of the impact of the heart against the chest wall. We wish to emphasize the importance of this definition of the heart murmur: that it must have appreciable duration after the first heart sound. With this understanding a good deal of confusion can be avoided.

A murmur of intensity "2" may be called a slight murmur. Inasmuch as the examiners in this study were well trained and exercised considerable care in auscultation, it is fair to say that murmurs of the first intensity (grade "1") are probably overlooked or not heard for the most part in routine general practice. It follows, therefore, that what has been called a murmur of grade "2", probably corresponds to what the general physician might term a faint systolic murmur. A murmur of grade "3" would have moderate intensity. One of grade "4" would be loud, while "5" and "6" would be very

loud and the loudest possible murmurs, respectively. There naturally are comparatively few cases with murmurs of the intensity of "5" or "6".

After a little experience and by thinking in the above terms, observers learn very quickly to gauge the intensity of murmurs with such accuracy that they do not differ in their estimates by more than one gradation, and frequently even agree completely. The same observer would in fact find very satisfactory accord in his designation given to a heart murmur in a patient examined from week to week. This matter of terminology has been gone into in some detail because we feel that the use of uniform terms is absolutely essential to success in any attempt to bring some order out of chaos in this complicated question of the significance of the systolic murmur.

The customary interpretation of the apical systolic murmur of moderate intensity is that it is due to regurgitation of blood through the mitral valve. If there is found additional evidence of valvular disease such as signs of mitral stenosis, or if the patient is known to be rheumatic, this regurgitation is regarded as organic and due to a structural change of the mitral valve. On the other hand, if the patient is not rheumatic and shows evidence of the degenerative form of cardiovascular disease such as hypertension, coronary artery symptomatology, and the like, the systolic murmur is looked upon as the result of a relative dilatation of the mitral ring, resulting from a dilatation of the left ventricle so that normal leaflets fail adequately to close the mitral orifice. It also has been thought that, either as a result of

changes in the character of the blood or because of dilatation of the myocardium, a similar systolic murmur might be present with anemia. Although the explanations are varied and obscure, it likewise has been believed that systolic murmurs can develop as a result of fever, emotion, hyperthyroidism, hypertension, and increased heart rate.

It has occurred to us that one of the factors in the production of a systolic murmur which has been very much neglected in our teaching of clinical medicine is the speed of blood flow. Systolic murmurs are frequently found in the same conditions in which, as Blumgart⁸ has shown, the rate of blood flow (not the heart rate) is also increased. In hyperthyroidism, after effort, and in pernicious anemia, systolic murmurs are common and the rate of blood flow is increased. Here the murmur cannot be due to dilatation of the heart, for X-ray studies have shown that the heart after effort and during hyperthyroidism is not dilated and may even be smaller. In some of the other conditions, such as fever, emotion, neurocirculatory asthenia, etc., may not a systolic murmur which is occasionally present be due to a similar mechanism, even if the increased speed of the ejection of blood is limited to the short distance from the heart to the large branches of the aorta? In other words, may not the snapping method by which the blood is expelled from the heart in these hyperactive states in some way cause a systolic murmur, apart from the factor of dilatation?

Furthermore, in the interpretation of systolic murmurs it is of import-

ance whether the murmur is present in the apical region or at the base of the heart, and whether it is heard with the patient recumbent or upright. Recently it has become the custom on the part of many physicians to listen to the heart after effort or during the held expiration. We have attempted to analyze all these factors in the production of the systolic murmur.

In a study of this sort, in which the objective finding that is being analyzed is one detected by auscultation, it is of some interest to compare our observations with those obtained by other physicians. For this purpose a comparison was made between the detection of murmurs by the house officers of the Peter Bent Brigham Hospital and our own observations on the same patients. As has been mentioned above, a systolic murmur, as we define it, must have an appreciable duration after the first heart sound; and what some observers might call a murmur we merely regard as a prolonged first sound, because there is no true bruit lasting into systole. We expected to find no murmurs at all where others had found systolic murmurs because it has become the habit of some house officers and students to say that a systolic murmur is heard, knowing that no great importance will be attached to that finding and fearing that some one else will hear a murmur which they have not noted. The findings in 427 cases were compared for this particular analysis. In 331, or 77 per cent, there was agreement between our observations and those of the house officers. In 28 cases, or 7 per cent, we found a systolic murmur when none was previously noted, and in 68 cases, or 16 per

cent, we failed to find a murmur when it was previously thought to be present. In four of these latter cases what was thought to be a systolic murmur was designated by us as a prolonged first sound. Although in a few instances it is reasonable to assume that a murmur may have been present at one time and not at another, the above discrepancy probably depends upon more careful auscultation and close adherence to the definition of a systolic murmur.

PROLONGED FIRST HEART SOUND

Reference has been made concerning the use of the term prolonged first heart sound. Frequently patients are thought to have a systolic murmur when on careful auscultation one really can hear no bruit extending into systole, during the interval between the first and second sounds. We have found in these cases that the phenomenon consists of a prolongation of the first sound but that systole itself is clear. This seems to be more common in thin-chested individuals and where the heart action is hyperactive, but not necessarily fast. There were 47 instances in these 1000 patients in which a prolonged first sound was heard. Twenty-five were males, and 22 were females. Although in different individuals the prolonged first sound was heard sometimes at the apex and sometimes at the base, and with the patient sometimes recumbent and sometimes upright, it was most usually found at the apex and with the patient lying down. Of these 47 cases, six had hypertension, four had definite fever, eleven had a pulse over 100, three had a hemoglobin less than

60 per cent, six were over 60 years of age and eight were under twenty. It would not seem, therefore, that the prolonged first sound had any clinical significance.

INCIDENCE OF MURMURS IN RELATION TO AGE, SEX AND LOCATION

In this series of 1000 cases there were 471 males and 529 females. The ages varied from infancy to old age. The distribution through the various decades is indicated in table 1. Throughout the decades there was no significant variation in the sexes except in the last two decades where the males predominated. The average age of the males was 39.4 and that of the females 34.6 years.

There were 196 of these 1000 patients who showed a systolic murmur of grade 1 or 2. Those having louder murmurs make up a special group which will be discussed below, where it will be evident that all cases with murmurs louder than grade 2 have organic cardio-vascular disease. Murmurs of fainter intensity, which one might call "functional" murmurs, therefore were present in 19.6 per cent of our series. This figure, however, will be very much reduced when the cases are more carefully analyzed, ruling out further instances of organic disease. Of these 196 patients there were 132 females and 64 males. This indicates that systolic murmurs of this type are about twice as frequent in females as in males. The distribution of these patients with murmurs throughout the various decades is indicated in table 2. It can be readily seen that the predominance of females with murmurs in

this group obtains in most of the decades up to the age of 60. This is especially true between the ages of 20 and 29, merely because there were so many normal nurses included in this study. The average age for the males is 43.0 years and for the females 36.2 years. Both of these figures are somewhat higher than the average of the

about 20 per cent will have a systolic murmur of low intensity and that this will be distributed somewhat unevenly throughout the various ages, with a definite preponderance in the female sex, and with the lowest incidence in males between the ages of 20 and 49 years.

The location of the murmur now

TABLE I
DISTRIBUTION OF 1000 PATIENTS BY AGE AND SEX

Decades	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Patients	2 M* 0 F	33 M 31 F	52 M 43 F	45 M 67 F	45 M 63 F	69 M 70 F	52 M 49 F	22 M 11 F	9 M 0 F
Children	31 M 35 F	4 M 0 F	—	—	—	—	—	—	—
Tuberculous..	—	0 M 1 F	17 M 14 F	10 M 13 F	12 M 5 F	14 M 5F	6 M 2 F	1 M 0 F	—
Doctors	—	—	43 M 0 F	3 M 0 F	1 M 0 F	—	—	—	—
Nurses	—	0 M 18 F	0 M 99 F	0 M 3 F	—	—	—	—	—
Total M	33	37	112	58	58	83	58	23	9
Total F	35	50	156	83	68	75	51	11	0
Total	68	87	268	141	126	158	109	34	9

*(M = males; F = females)

entire 1000 cases (39.4 years and 34.6 years, male and female ages, respectively).

The percentage of murmurs in the different decades varied somewhat but ranged approximately between 15 per cent and 25 per cent. There was a definite diminution in this percentage between the ages of 20 and 50, with a greater incidence during the first two and the last few decades (table 2). The lowest incidence, 7.0 per cent (table 3), was found in the group of males between the ages of 20 and 49. It therefore can be seen that, of a large group of routine, unselected patients,

needs to be considered. The two areas studied were the apex and the base of the heart. No differentiation was made as to whether the murmurs were audible in the pulmonic or aortic areas. For the most part it was in the pulmonic area that these basal murmurs when present were prominent, except in the older group where basal murmurs were generally aortic. Of the 196 patients who showed a systolic murmur, in 122 it was present at the apex and in 145 at the base of the heart. In many it was present in both areas. The distribution of these murmurs according to location throughout

TABLE II
INCIDENCE OF SYSTOLIC MURMURS IN VARIOUS GROUPS EXAMINED

Decades	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Patients	1 M* 0 F	7 M 6 F	2 M 4 F	2 M 15 F	6 M 12 F	12 M 20 F	13 M 13 F	7 M 0 F	— —
Children	4 M 12 F	2 M 0 F	— —	— —	— —	— —	— —	— —	— —
Tuberculous	— —	— —	3 M 5 F	0 M 3 F	0 M 1 F	0 M 1 F	1 M 0 F	— —	— —
Doctors	— —	— —	3 M 0 F	1 M 0 F	— —	— —	— —	— —	— —
Nurses	— —	0 M 2 F	0 M 31 F	— —	— —	— —	— —	— —	— —
Total M	5	9	8	3	6	12	14	7	0
Total F	12	8	40	18	13	21	13	7	0
Total	17	17	48	21	19	33	27	14	0
Percentage	25%	19.5%	17.9%	14.2%	15.8%	20.9%	24.8%	41.2%	0

*(M = males; F = females)

TABLE III
PRESENCE OF MURMURS IN RELATION TO AGE, SEX, LOCATION AND INTENSITY

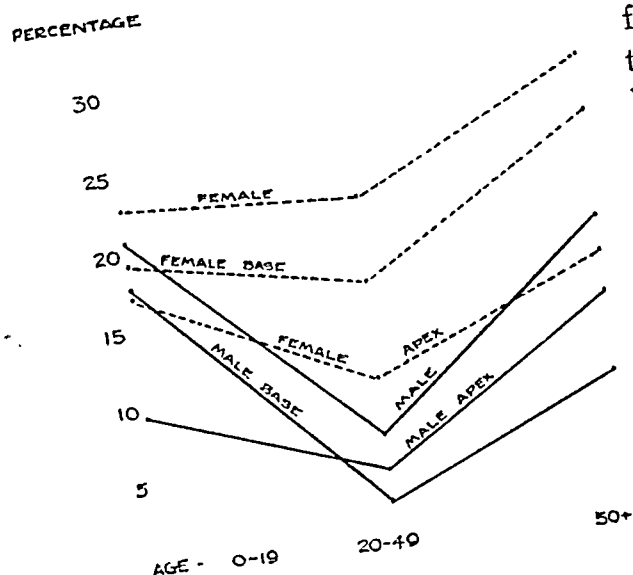
	0-19 yrs.				20-49 yrs.				50 + yrs.			
	Males		Females		Males		Females		Males		Females	
No. Examined	70		128		228		264		173		137	
No. with Murmurs	15		30		16		60		34		41	
% with Murmurs	21.4		23.4		7.0		22.7		19.7		29.9	
No. with Murmurs at Apex and Base	Apex	Base	Apex	Base	Apex	Base	Apex	Base	Apex	Base	Apex	Base
	7	13	23	25	12	8	30	46	26	17	24	36
% with Murmurs at Apex and Base	10.0	18.6	18.0	19.5	5.3	3.5	11.4	17.4	15.0	9.8	17.5	26.3
Intensity Index*	1.21	1.27	1.48	1.42	1.38	1.25	1.42	1.30	1.44	1.27	1.14	1.43

*(Method of calculating the index explained in text)

the various decades and in the two sexes is indicated in table 3. It is evident from this table that the systolic murmurs at the apex were about one and one-half times as common as at the base in males over 19 years of age. Of 401 males over 19 years old, there were 38 apical and 25 basal systolic murmurs, i.e., 9.5 per cent and 6.2 per cent respectively. The reversed re-

lation held for 401 females, where systolic murmurs predominated at the base, the figures being 20.4 per cent and 13.5 per cent respectively. In the first two decades (table 3) the above relation did not hold, for in males of the younger group, basal systolic murmurs were almost twice as frequent as apical. These relations are graphically illustrated in table 4.

TABLE IV
A GRAPHIC ILLUSTRATION OF FIGURES
SHOWN IN TABLE 3

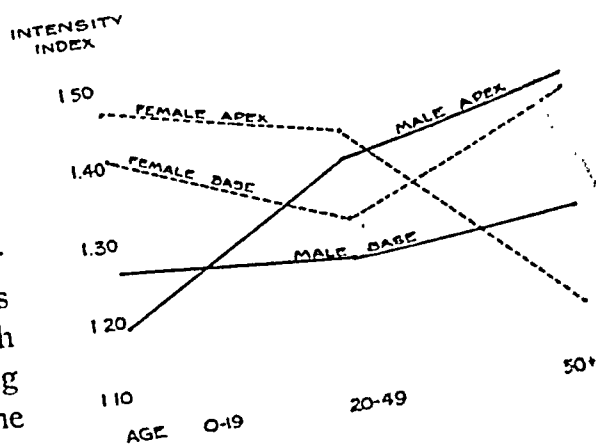


INTENSITY OF MURMURS IN RELATION TO AGE, SEX, AND LOCATION

As has been stated above, in these 196 cases were included only those that showed a systolic murmur of grade 1 or 2, whether it was heard at the apex or base of the heart. It seemed to be of some interest to determine whether the intensity of the murmur was greater in one region than in the other and whether there were any variations in the intensity either with sex or with age. A figure was obtained indicating the intensity of the murmur at the apex or base of the heart for any group of cases in the following manner. There were, for instance, 23 females under the age of 20 who had apical systolic murmurs. There were 11 of these with murmurs of grade 2 and 12 with murmurs of grade 1. That made a total count of 34 ($11 \times 2 + 12 = 34$). The intensity index therefore was 1.48 (34 divided by 23). In a similar manner, figures were

obtained for males and females in the three age groups of 0-19, 20-49 and over 49 years. These results are shown in table 3. This table indicates that in females apical murmurs are louder than basal in the first two age groups but become less loud in the older group. The apical murmurs in males, on the other hand, increase in intensity with advancing years. Furthermore, the intensity of apical murmurs is less in males than in females during the first two decades. The intensity indices for the apical murmur in females are 1.48, 1.42, 1.14 for the three age groups respectively, those for males being 1.21, 1.38, 1.44. These results are graphically shown in table 5.

TABLE V
A GRAPHIC ILLUSTRATION OF FIGURES
SHOWN IN TABLE 3



It must be of some significance that apical murmurs of the type analyzed in this study diminish in intensity with increasing years in females, although the actual incidence is not materially different throughout the decades (table 4). One might infer from this that an apical systolic murmur of grade 2 would not only be less com-

mon in elderly females but would have more importance when present.

EFFECT OF POSITION ON SYSTOLIC MURMURS

Throughout this study wherever possible (about 900 cases) notations were made whether murmurs were present at the apex and base of the heart with the patient recumbent as well as upright. The purpose of this was to compare the intensity of systolic murmurs under various circumstances. The relative frequency of apical and basal murmurs has already been discussed. Of the 196 patients with grade 1 or 2 murmurs, 167 were examined while recumbent and upright. The remaining 29 were examined only while recumbent. Of the patients examined in the two positions, 71.2 per cent showed a basal systolic murmur with the patient recumbent, and in 61.3 per cent it was present in this location in the upright position. At the apex, 62.3 per cent showed a murmur in the recumbent position, and only 54.8 per cent had the murmur in the upright position. Thus it is seen that for murmurs of grades 1 and 2, the most common location is at the base with the patient recumbent, and the least common is at the apex with the patient upright. The intensity of the murmurs followed fairly closely the percentages just given for the incidence, the loudest being at the base recumbent and the faintest at the apex upright. It must not be inferred that the same relations hold for murmurs customarily heard with organic heart disease, for these "organic" murmurs are more common at the apex than at the base of the heart.

EFFECT OF HELD EXPIRATION ON PULMONARY SYSTOLIC MURMURS

The findings in the pulmonic area during held expiration we believed needed investigation. Many physicians auscult the heart carefully for murmurs while the patient holds the breath in expiration. This is done to avoid the confusion of respiratory sounds and to have the heart nearer the chest wall by displacing the overlying lung. To study this point more carefully, 22 normal individuals were examined during normal quiet breathing and during held expiration. In none of these were murmurs heard during normal breathing. In one a systolic murmur of grade 1 and in another a murmur of grade 2 were present in the pulmonic area during the held expiration. This same finding has been frequently noted in the larger group of cases included in this study. Furthermore, systolic murmurs were also frequently found to be accentuated by this method. We therefore feel justified in concluding that although a held expiration may uncover a diastolic murmur not otherwise heard at the base of the heart, the appearance of a systolic murmur in this location during this maneuver is of no importance.

SYSTOLIC MURMURS AFTER EFFORT

It has become the custom in recent years for physicians to examine the heart before and after effort for the purpose of detecting murmurs. Various exercises have been used as functional tests of the heart. As a result of this, notations have been made of a systolic murmur or an irregularity disappearing or developing after these exercises. It is not the purpose of this

discussion to take up functional tests in general, but to comment on the appearance of a systolic murmur after effort. Many examiners for life insurance companies have occasionally found systolic murmurs after prescribed exercise tests and on the basis of this have either refused the applicant insurance or have increased his rating. We therefore studied ten normal physicians ranging in age from 24 to 41 before and after a brisk effort. The exercise consisted of running rapidly for about 100 yards. In none of these was a systolic murmur present before the exercise. Within one minute after the exercise and with the pulse ranging from 122 to 176, nine of these ten individuals showed a systolic murmur of grade 1 or 2 at the apex or base of the heart. Generally the murmur was present in both areas and for the most part it was louder in the pulmonic area. At the end of two or three minutes the murmurs all diminished in intensity or disappeared. Although the effort here was much more violent than that required in the usual tests in physicians' offices we feel quite definitely that a systolic murmur that appears after effort, when it was not present before the test, has absolutely no significance and may be found in most normal people.

ANALYSIS OF MURMURS OF GRADES 3 AND 4 INTENSITY

The group of patients with a systolic murmur of greater than grade 2 requires detailed analysis. There were 14 instances in which the murmur had a grade 3 intensity and five instances of grade 4. For the most part these patients were found in the medical

wards. In order to have a fairer distribution of our cases and not to exclude a legitimate proportion of patients with heart disease, 100 patients on the medical service were included, among whom one would naturally expect to find a fair number with organic heart disease. These are the cases that furnish most of the data concerning murmurs of greater than grade 2 intensity. In practically all of these cases the systolic murmur was as loud or louder at the apex than at the base of the heart. In one patient with congenital heart disease, the intensity of the murmur was greatest in the pulmonic area, and in one of the hypertensive cases the murmur was louder over the aortic area than at the apex.

Among the patients with grade 3 murmurs there were seven who had distinct hypertension, one of which had an additional luetic aortic insufficiency. Three additional cases had organic rheumatic valvular disease and one had myocardial failure following coronary thrombosis. Of the remaining three, one had suffered a violent hemorrhage from a gastric ulcer reducing the red blood count to 2,200,000 and shortly later was found to have well marked hypertensive heart failure. One had chronic nephritis with a red blood count of 2,000,000; and the third was a luetic patient who had thyrotoxicosis and cardiac hypertrophy. Of the five patients with a systolic murmur of grade 4, four had well marked rheumatic valvular disease, and one had congenital patent ductus arteriosus. It is evident from the above analysis that the louder systolic murmurs for the most part are

due to organic valvular, hypertensive, or myocardial heart disease that can be definitely recognized, and that systolic murmurs of this intensity only occasionally result from a severe anemia or its accompanying cause.

ANALYSIS OF MURMURS OF GRADES 1 AND 2 INTENSITY

One of the important parts of this study is the consideration of some of the clinical factors that may either be responsible for, or in some way be related to, the systolic murmurs of grades 1 and 2 which were present in 196 cases. The factors particularly studied were hypertension, anemia, hyperthyroidism, a past history of rheumatic fever, chorea or scarlet fever, definite evidence of organic heart disease, and age. In a small number miscellaneous conditions like syphilis, the presence of fever, etc., were considered. There were 40 instances of hypertension, of which 17 were under 50 years of age. It is quite well known that patients with hypertension may or may not have a systolic murmur. It is generally accepted that as a group, people with hypertension will show a systolic murmur more often than normal individuals. Indirect evidence for this view was found in this study. The average readings of 179 consecutive patients in this study not showing murmurs were 129 mm. of mercury systolic and 79 mm. diastolic. The average readings for 115 consecutive patients with murmurs of grade 1 or 2 were 144 mm. of mercury systolic and 84 mm. diastolic. This difference is real and indicates that hypertension is a factor in the production of the systolic murmur.

Thirteen of the 196 cases had anemia (red blood count under 3.5 million), of which six had no other factor of importance to account for the murmur. Nine had hyperthyroidism and one of these had rheumatic fever in addition. It is very significant that twelve had a definite history of rheumatic fever or chorea and sixteen others had evidence warranting suspicion of a previous rheumatic state in that they had early growing pains, vague rheumatics, frequent spontaneous epistaxis, and repeated sore throats. We know that many rheumatic patients have no more definite past history than is indicated by the above symptoms. There is no doubt in our minds that many of these cases were rheumatic patients and that the systolic murmur had more than an accidental significance. In twelve cases there was a past history of scarlet fever, in eight of which other factors were present which may have had some bearing. We feel that scarlet fever is occasionally responsible in some individuals for the presence of a systolic murmur, but that in such cases one can generally also find evidence suggestive of rheumatism.

Definite organic heart disease was found in 18 of these patients, ten of whom had valvular and eight non-valvular heart disease. This group needs no further explanation for it is common knowledge that heart disease in one form or another may be accompanied by murmurs of this intensity.

In studying the question of age as a factor in the production of systolic murmurs we found 19 cases who were over 50 years of age and in whom none of the other factors mentioned

above could be held responsible for the murmurs. Some of these no doubt had cardio-vascular disease of which we were not aware, for cardiac enlargement and coronary artery disease could easily have escaped our attention in this routine study.

There remained 74 patients with a systolic murmur not explained by the above factors. Of these there were 29 in which there were suggestive influences that might have a bearing on the production of a murmur, such as tertiary syphilis, leukemia, displaced heart, etc. In fact there were 16 with a definite fever, and we believe that in some instances the hyperactivity of the heart accompanying fever may be responsible for a murmur that disappears with the return of the temperature to normal. There remained, however, 45 patients with a systolic murmur in whom not even the additional factors just mentioned were present. In some of these cases the data such as blood counts, blood pressure reading, and past history of rheumatic disease were not available. It is interesting that only 11, or 24 per cent, of these 45 patients with an unexplained murmur had a murmur of grade 2, whereas in the entire group of 196 patients with murmurs 77, or 39 per cent, had grade 2 murmurs. This means that for the most part murmurs that have no definite or suggestive explanation for their presence are apt to be of the faintest intensity.

Of these 45 patients with unexplained systolic murmur 13 were males and 32 were females. The systolic murmur was confined to the apex in 12 cases, to the base in 25 and was present at both areas in 8. This bears

out the impression obtained from studying the entire group that faint, unexplained and what might be considered insignificant systolic murmurs are most common at the base of the heart in the female sex. In fact the comparative frequency of systolic murmurs in nurses (28 per cent) increased the total incidence appreciably, for systolic murmurs of grade 1 or 2 were only present in 19 per cent of the patients in the surgical wards of the hospital.

From the above analysis it follows that only 4.5 per cent of 1000 patients had a systolic murmur that could not be explained by some fairly definite clinical cause and that only 1.1 per cent had such an unexplained murmur which was louder than the very faintest that can be heard. If more were known of these cases their numbers would probably be still less. These murmurs can rightly be called "functional" or benign, although many of the other systolic murmurs that had a definite clinical cause (such as those with hyperthyroidism, anemia, etc.) might also be called functional in the sense that the valves were not diseased.

While we agree with McCrudden⁶ that the average life expectancy of patients with systolic murmurs is definitely diminished, we believe that if from a series of such cases one rules out those showing the presence of such causative factors as heart disease, hypertension, hyperthyroidism, etc., there will remain a group in which this prognostic rule will not hold true. In other words, while the life expectancy for our group of 196 patients with grade 1 or 2 systolic murmurs probably is lower than for a similar group without

murmurs, we do not believe an appreciable difference will occur in the final 45 cases of the 196, in whom no explanation could be found for the murmur. This is especially true for the 34 of these 45 cases in whom only the faintest murmur could be heard.

It must not be inferred from this detailed study of the systolic murmur and from the emphasis that has been placed on attempts to correlate such murmurs with definite clinical conditions that murmurs need indicate serious disease, nor that they even indicate heart disease. Patients with heart disease and loud murmurs may be in better health and live longer than other patients with heart disease without murmurs or with faint murmurs. It must be borne in mind that there are many patients with murmurs who have no heart disease at all. The main purpose of this study is to show that systolic murmurs often have a clinical explanation. Furthermore we believe that a systolic murmur of greater than grade 1 intensity should be regarded with suspicion and that a proper interpretation of systolic murmurs will lead to more intelligent diagnosis, prognosis, and treatment of disease.

SUMMARY AND CONCLUSIONS

An analysis was made of the incidence and significance of systolic murmurs in 1000 consecutive individuals distributed as follows: 663 patients in the surgical wards of the Peter Bent Brigham Hospital, 100 patients in a tuberculosis sanitarium, 47 healthy house officers and medical students, 120 nurses, and 70 infants and children in the wards of the Children's Hospital. It quickly became evident

that no progress in such a study could be made unless the systolic murmur were accurately defined and the intensity of the murmur were estimated. By a systolic murmur we mean a distinct bruit that is heard definitely following the first heart sound and extending appreciably into systole. This excludes sounds that are often called systolic murmurs but which are merely impurities or prolongations of the first heart sound. As to intensity, we have divided murmurs into six gradations. Grade 1 is the faintest definite murmur of the type that although distinct will not be heard unless auscultation is most carefully done. Grade 6, although extremely rare, is the type in which the murmur can be heard without a stethoscope and away from the patient's chest. Grade 2 is probably of that slight intensity which in ordinary auscultation not expertly practised, would be called a faint or slight murmur. Grades 3, 4, and 5 might correspond to the terms moderate, loud, and very loud. This method of gradation is practical. Different observers will agree very closely in their estimation of murmurs.

There were 47 instances in these 1000 patients in which a prolonged first heart sound was heard. Although present at times at both the apex and base of the heart with the patient recumbent or upright it was most common at the apex with the patient lying down. This sound was not found to have any clinical significance.

There were 196 cases, or 19.6 per cent, that showed a systolic murmur of grade 1 or 2. The murmur was present about twice as frequently in females as in males. The average age

of those with murmurs was 43.0 years for the males and 36.2 years for the females. The incidence of the murmur in the different decades varied somewhat. The lowest incidence was found to be in males from 20 to 49 years.

A study was made as to the relative frequency of murmurs at the apex and base of the heart. Apical murmurs were one and one-half times as frequent as basal in males and the reverse relationship obtained for females.

A method was devised to obtain an index of the intensity of the murmurs heard at the apex and base of the heart in the two sexes and at different ages. It was found that apical murmurs of grades 1 and 2 diminish in intensity with increasing years in the females, but that in males apical murmurs increase in intensity with increasing years.

Wherever possible patients were examined in both the recumbent and the upright positions. In this group of 196 patients it was found that murmurs of grades 1 and 2 were most common with the patient recumbent and least common at the apex with the patient upright.

In 22 consecutive individuals who had no murmurs on ordinary examination, there were 2 who had a systolic murmur in the pulmonic area during a held expiration. We believe that this procedure, although it may uncover a significant diastolic murmur, has no clinical importance in relation to a systolic murmur.

Ten normal physicians without murmurs were examined before and after a brisk effort. In nine a murmur of grade 1 or 2 was present either at the apex or base of the heart one or two

minutes after the effort. We believe that a murmur not previously present, brought out by this method, is a normal phenomenon.

In these 1000 cases, there were 14 with murmurs of grade 3 intensity and five of grade 4. In every instance, organic disease was found, adequate to explain the murmurs. Of the 14 with grade 3, seven had well marked hypertension, three had rheumatic valvular disease, one had a coronary thrombosis, one had marked anemia with a red cell count of about 2,000,000, one had marked anemia and myocardial failure and one had syphilis, thyrotoxicosis, and marked cardiac hypertrophy. Four of the five patients with grade 4 murmurs had rheumatic valvular disease and the other had congenital patent ductus arteriosus. We therefore feel that the louder systolic murmurs can never be dismissed as insignificant.

In an attempt to discover how many patients have a systolic murmur not associated with any important disease, past or present, it was found that of 196 who had murmurs of grade 1 or 2, 40 had hypertension, 13 had anemia, 9 had hyperthyroidism, 12 had a definite past history of rheumatic fever or chorea and 16 had a suspicious history of a previous rheumatic state. There were 12 cases with a past history of scarlet fever. We believe that all the above factors may have some relation to the murmurs present. There were 18 cases with definite organic heart disease, 10 valvular and eight non-valvular. There were 19 cases over 50 years of age in which none of the above factors except age were present. In some of these no doubt, cardio-vascular disease existed which we did not

detect. There were 29 cases in which suggestive influences which might have a bearing on the production of the murmur were present such as tertiary syphilis, leukemia, displaced heart, etc. In fact 16 of these had a definite fever. Finally there remained 45 patients (4.5 per cent) in whom none of the definite or possible influences in the production of the murmur could be elicited. Only 11 (1.1 per cent) of these had murmurs of grade 2.

In conclusion we wish to speak against the prevailing opinion that systolic murmurs have little or no significance and to emphasize the fact that although they are frequently present in the absence of heart disease, a proper interpretation of the intensity of the murmur and of the possible causative factors considered above will aid greatly towards more accurate diagnosis, prognosis, and treatment of disease.

REFERENCES

- ¹CABOT, R. C.: Facts on the heart, 1926, W. B. Saunders Co., Philadelphia, pages 291 and 296.
- ²HERRICK, J. B.: In defense of stethoscope, *ANN. INT. MED.*, 1930, iv, 113-116.
- ³WHITE, P. D., in CECIL, R. L.: Textbook of medicine, 2 Ed., 1930, W. B. Saunders Co., Philadelphia, page 1095.
- ⁴THAYER, W. S.: Reflections on the interpretation of systolic cardiac murmurs, *Am. Jr. Med. Sci.*, 1925, clxix, 313-321.
- ⁵LEE, R. I.: The physical examination of apparently healthy individuals; its importance, limitations and opportunities, *Boston Med. and Surg. Jr.*, 1923, clxxxviii, 929-937.
- ⁶McCRUDDEN, F. H.: Heart murmurs and insurance, *New Eng. Jr. Med.*, 1931, cciv, 598-600.
- ⁷WHITE, P. D.: Clinical significance of apical heart murmurs, *Am. Jr. Med. Sci.*, 1927, clxxiv, 731-738.
- ⁸BLUMGART, H. L.: Velocity of blood flow in health and disease; velocity of blood flow in man and its relation to other measurements of circulation, *Medicine*, 1931, x, 1-75.

Apoplexy*†

A Study of 801 Cases Admitted to the Kings County Hospital During the Five Years from 1923 to 1928

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A STUDY has been made of all the cases of apoplexy admitted to the Kings County Hospital during the five years, 1923-1928. Several important factors must be borne in mind in considering this material. The Kings County Hospital is a city hospital and the largest in the Borough of Brooklyn. Its ambulance service covers the largest area served by any hospital in the borough and in addition many patients are brought to Kings County Hospital by the ambulances of other hospitals. These conditions result in the admission of a large number of cases of apoplexy. The patients fall into one of two groups. In the first, the patient has been stricken at his work, or on the street, or perhaps in the home and is admitted shortly after the onset. In the second group we find those patients who have been cared for in the home for from a few days up to a week or more and are admitted to the hospital because they have not shown satisfactory improvement.

In this study only those cases were included in which a definite diagnosis

of vascular accident was made. Not all of the patients presented symptoms or signs of motor involvement. In the five year period selected, 801 cases were found to fall into this group.

It has been noted by previous investigators in this field that the importance formerly attributed to certain etiologic factors was much exaggerated. For example, it is now recognized that it is exceptional for any of the cerebral vascular accidents, even hemorrhage, to occur during great exertion. Natural acts involving effort, such as defecation and coitus, and even mental excitement are considered of very little importance as precipitating factors. There are other factors which are matters of discussion and dispute. Foremost among these debatable points are: the influence of the season of the year on the frequency of vascular accidents; the predominance of such lesions in the male or the female; the question as to which cerebral hemisphere is most often affected; the relation of the height of the blood pressure to such lesions; the connection between syphilis and apoplexy; and the age period in which the highest incidence of apoplexy is found. In the study presented in this paper data bearing on these disputed points are

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presented. To reach definite conclusions a much larger group of cases must be subjected to analysis, but I believe that it is important to add our series of cases to the literature for future reference.

AGE

No period of life is exempt from cerebral hemorrhage, but inasmuch as arterial degeneration is most common in the later periods, it is after middle life that we find the chief liability to apoplexy. On this point, however, there seems to be some want of agreement in the published statistics.

The following tabulation is from the postmortem records of St. Bartholomew's Hospital, and is based on 124 cases of intracranial hemorrhages in which the age was ascertained.

AGE	MALE	FEMALE	TOTAL	PCT.
8-20	6	2	8	6.4
21-30	4	3	7	5.6
31-40	11	6	17	13.7
41-50	32	11	43	34.6
51-60	18	6	24	19.3
61-70	14	6	20	16.1
71-80	5	0	5	4.0
Total	90	34	124	

From this table the liability to apoplexy seems to be greatest in the period between forty and fifty and to decline appreciably with each succeeding decade.

We must not overlook the fact that cerebral hemorrhage may occur in very early life. Potts² states that the fact that apoplexy is not infrequent in early life does not seem to be generally recognized. In the statistics collected by Thomas from the records of the Johns Hopkins Hospital, 135 out of 740 cases occurred during the

first ten years of life, a number greater than during any subsequent decade until the fifth.

Gintrac's³ figures have been freely quoted by succeeding authors. According to Gintrac's tables the percentage of cases increases with each decade from the age of thirty to attain its maximum between sixty-one to seventy. It is also noticeable that as many as 17 per cent fall between seventy to eighty.

In our series of cases (table 1) birth hemorrhages have not been included. The first cases to be noted occurred between the ages of twenty to twenty-four. Only one case fell in the age period between ninety-six to one hundred and none was over one hundred years of age.

TABLE I

AGE OF PATIENT AT TIME OF VASCULAR ACCIDENT

Age	1923	1924	1925	1926	1927	Total
20	0	1	0	0	2	3
24	3	2	0	0	2	7
28	2	2	2	2	3	11
32	1	2	2	1	2	8
36	4	5	2	4	5	20
40	9	6	16	7	7	45
44	12	17	6	7	10	52
48	11	15	7	14	13	60
52	16	20	18	17	12	83
56	21	21	27	17	11	97
60	17	35	17	17	34	120
64	17	18	26	20	19	100
68	16	20	15	15	15	81
72	6	9	14	9	14	52
76	6	4	3	8	2	23
80	6	1	4	7	7	25
84	1	1	0	1	1	4
88	0	0	0	5	0	5
92	1	0	0	1	2	4
96	0	0	0	0	1	1
100	0	0	0	0	0	0
Total	149	179	159	152	162	801

Study of this table shows that there is a gradual increase in the number of cases from the age of thirty-six up to sixty-four and a decline thereafter. If we examine each year separately we notice that this same finding is consistent. Two hundred and twenty cases, or 29.9 per cent, occurred between the ages of sixty to sixty-eight. We find only 49 cases between the ages of twenty and forty.

BLOOD PRESSURE

In the total of 801 cases, the blood pressure was taken in 647 cases. There seems to be the impression among many physicians that apoplexy is usually associated with very high blood pressure. Table II shows the number of cases for each ten points rise of systolic pressure, separately for each year in order to show how consistent these figures seem to be.

We find the number of cases increasing with the increase of blood pressure from 100 up to 140 millimeters of mercury. The total number of cases with systolic blood pressures of 140 millimeters of mercury or less was 105, which is 16.2 per cent of the total group. In the group with systolic blood pressures between 140 and 170 millimeters of mercury there were 205 cases, or 31.6 per cent. These figures indicate that the belief that very high blood pressure is essential for apoplexy is inaccurate.

SYPHILIS

Of the 801 cases, 617 had a Wassermann test done during their stay in the Hospital. In table 3 is shown, arranged by year, the number of patients who had positive and negative

TABLE II
SYSTOLIC PRESSURE TAKEN ON ADMISSION
TO HOSPITAL

Pres- sure	1923	1924	1925	1926	1927	Total
100	4	6	0	1	5	16
110	3	5	7	3	5	23
120	7	8	8	3	8	34
130	9	8	7	4	4	32
140	14	11	17	13	16	71
150	13	19	16	4	10	62
160	14	18	24	12	14	72
170	9	13	12	13	10	57
180	11	9	9	18	13	60
190	13	13	3	12	11	52
200	3	11	10	8	9	41
210	3	5	7	10	12	37
220	1	5	13	10	7	36
230	3	4	0	4	5	16
240	2	2	7	0	1	12
250	0	2	3	1	5	11
260	2	1	2	0	3	8
270	0	1	1	1	0	3
280	0	1	0	0	0	1
290	0	1	0	0	0	1
300	0	0	1	1	0	2
310	0	0	0	0	0	0
Total	111	143	147	118	138	647

Wassermann tests. The average age of those who had positive Wassermann tests, whether they died or improved during their stay in the Hospital, and their average systolic pressure, are also indicated in this table.

The fact that a positive blood Wassermann test was obtained in only 8.58 per cent of 617 cases of apoplexy investigated is evidence against the belief of some that syphilis plays a considerable rôle in the causation of this condition. The high mortality in this group may perhaps be explained as follows. The most common vascular lesion of the brain due to syphilis is an endarteritis and thrombosis resulting in

softening. Thrombosis, as Jones⁶ has shown in a series of 143 autopsied cases, is twice as apt to occur during sleep as is hemorrhage. It may be presumed that many of these cases therefore occurred in the patients' homes and it would be in accord with our experience that they would not be transferred to this Hospital from the

their stay in the Hospital for each month during the five years.

Even from as large a series as this, it is difficult to draw clean cut conclusions. However, it is evident that the admissions were fewest in number in July, August and September and that the largest number admitted was in January. From January to July the

TABLE III
RESULTS OF WASSERMANN TEST

Year	Negative Test	Positive Test					
	Number	Number	Per cent Positive	Died	Improved	Average Age	Average Pressure
1923	128	10	7.23	6	4	58.7	132.6
1924	148	13	8.07	8	5	59.8	131.6
1925	65	16	19.75	13	3	50.2	157.5
1926	83	5	5.68	5	0	54.0	149.7
1927	140	9	6.04	8	1	57.7	138.5
	564	53	8.58	40	13	56.08	141.9

home until their condition had become critical.

INFLUENCE OF SEASON

It seems to be accepted almost as an axiom that cold weather predisposes to cerebral hemorrhage if the blood vessels are diseased and the blood pressure is high. Tooth's¹ figures, however, show very little seasonal difference. Gintrac's figures sustain the impression that the accident is more likely to happen in the cold months. The theory that has been suggested is that the cold weather produces a contraction of the peripheral vessels and that consequently there occurs a rise of the blood pressure in the vessels of the internal organs. In table 4 there is recorded the number of cases admitted and the information as to whether these patients died or recovered during

number ran consistently high. As to the percentage of deaths, we find a variation. The mortality ran high from September to January 1st, but we also find a high death rate in March, May and July. If we are to consider the cold weather theory seriously we should expect a high mortality in January when the largest number of admissions occurred, since an increase of blood pressure would predispose to the more fatal accident of hemorrhage rather than to the less fatal one of thrombosis. Instead, we have in January the third lowest death rate.

INFLUENCE OF SEX

As to the predominance of sex, we find it quite agreed that men outnumber women. Jelliffe and White⁷ state that: "Men are more often affected

(seven to five) than women." Tooth says: "As to sex there can be no doubt that women are much less liable to cerebral hemorrhage than men." Reference to the table of Tooth shows 90 males (72.5 per cent) and 34 females (27.4 per cent). Here, perhaps, the statistics of the postmortem room of a

years are 56.1 per cent males to 43.9 per cent females. It is noteworthy that these are practically the same as Gintrac's figures.

SITE OF LESION

There is still a difference of opinion as to which side of the brain is most

TABLE IV
CASES ADMITTED EACH MONTH

Month	1923			1924			1925			1926			1927			Total Cases Admitted	Number Died	Improved	% Died
	Died	Improved	Total	Died	Improved	Total	Died	Improved	Total	Died	Improved	Total	Died	Improved	Total				
January	10	5	15	15	5	20	21	9	30	14	5	19	13	3	16	100	73	27	73
February	8	6	14	20	0	20	3	3	6	17	2	19	9	5	14	73	57	16	78
March	14	4	18	13	1	14	18	1	19	11	0	11	16	4	20	82	72	10	87
April	10	2	12	16	9	25	8	6	14	10	1	11	9	4	13	75	53	22	70
May	11	5	16	8	2	10	16	3	19	13	0	13	19	5	24	82	67	15	82
June	7	8	15	10	4	14	12	2	14	6	1	7	17	5	22	72	52	20	72
July	3	1	4	10	3	13	9	2	11	10	1	11	4	1	5	44	36	8	82
August	4	3	7	11	4	15	5	1	6	9	0	9	3	4	7	44	32	12	73
September	8	3	11	5	1	6	9	3	12	12	0	12	3	3	6	47	37	10	79
October	12	1	13	9	2	11	5	1	6	17	1	18	6	2	8	56	49	7	87
November	7	4	11	13	5	18	8	3	11	10	0	10	13	0	13	63	51	12	81
December	10	3	13	9	4	13	10	1	11	10	2	12	12	2	14	63	51	12	81
Total	104	45	195	139	40	179	124	35	159	139	13	152	124	38	162	801	630	171	

general hospital may lead to an erroneous conclusion. Many of the men are brought in from the street or from their work where they have fallen; women who are more likely to be seized at home are also more apt to remain at home. Perhaps Gintrac's conclusions are nearer the truth, namely, that the relation between male and female cases is about 57 per cent to 43 per cent.

The sex distribution of our cases is presented in table 5. The number of male patients runs consistently higher each year than that of the females. The average percentages for the five

TABLE V
SEX DISTRIBUTION OF CASES

Year	Male	Female	Pct. of Males
1923	86	63	57.7
1924	100	79	55.8
1925	87	72	54.7
1926	83	69	54.6
1927	94	68	58.0

commonly affected. From Morgagni's early dictum concerning the greater prevalence of right-sided hemorrhages general opinion has swung at the present time to the belief that the right and the left sides are about equally

involved. Jones's⁶ collection of 1733 cases showed an incidence of 53 per cent of lesions of the left hemisphere.

In the study of the cases in our series we find that 53.2 per cent of the patients who had involvement resulting in paralysis had a lesion in the left hemisphere resulting in a right hemi-

of the data brings out the following points of interest.

1. The largest number of cases, or 29.9 per cent, occurred between the ages of sixty to sixty-eight.

2. Of the 647 patients whose blood pressure was taken, 205, or 31.6 per cent, had systolic blood pressures of

TABLE VI
COMPARISON OF MOTOR INVOLVEMENT AND MORTALITY RATE

Year	Right Hemiplegia	Left Hemiplegia	No Paralysis	% of Right Hemiplegia	% of Deaths
1923	82	57	10	58.9	69.7
1924	89	76	14	53.3	77.6
1925	70	63	26	57.6	77.9
1926	51	50	51	50.4	92.1
1927	77	78	7	49.6	76.5

plegia. This figure is practically the same as that of Jones.

MORTALITY

The mortality in this series was 78.6 per cent, a figure not far from that reported for the large number of cases collected by Jones. This mortality rate seems high, but it is no doubt to some extent affected by the circumstances, already described, under which our patients with apoplexy were admitted to this Hospital.

Jones pointed out that the age and the sex made little difference in the death rate. Under sixty years of age 76.8 per cent of the males and 79.6 per cent of the females died, while over sixty years of age 75.7 per cent of the males and 82.4 per cent of the females died.

CONCLUSIONS

In this study of 801 cases of vascular accidents to the brain, the analysis

between 140 and 170 millimeters of mercury.

3. Of the 617 patients on whom a Wassermann test was performed, only 8.58 per cent had a positive Wassermann. Forty of the 53 cases that had a positive Wassermann died.

4. The hospital admissions of cases of apoplexy were least numerous in the months of July, August, and September, and most numerous in January.

5. The sex distribution in this series was 56.1 per cent males to 43.9 females.

6. Of the patients showing paralysis, 53.2 per cent had a lesion in the left cerebral hemisphere.

7. The mortality in this series for the five years was 78.6 per cent.

The author wishes to express his appreciation to Dr. William Browning and Dr. Arthur C. Brush for the opportunity of studying these cases.

REFERENCES

- ¹TOOTH, H. H., in ALLBUTT, C., and ROLLESTON, H. D.: A system of medicine, Vol. 8, 1910, Macmillan and Company Ltd., London, p. 309.
- ²POTTS, C. S.: Some mistaken ideas concerning apoplexy, Penn. Med. Jr., 1921, xxiv, 867-869.
- ³GINTRAC, E.: Maladies de l'appareil nerveux, 1869, ii, 467.
- ⁴OSLER, W. (quoted by THOMAS): Modern medicine, its theory and practice, 3 Ed., Vol. 1, 1925, Lea and Febiger, Philadelphia, p. 396.
- ⁵COLLIER, J., and ADIE, W. J., in PRICE, F. W.: A textbook of the practice of medicine, by various authors, 1922, xxxvi, H. Frowde; Hodder and Stoughton, London, p. 1355.
- ⁶JONES, A. E.: The onset of hemiplegia in vascular lesions, Brain, 1905, xxviii, 527-555.
- ⁷JELLIFFE, S. E., and WHITE, W. A.: Diseases of the nervous system; a textbook of neurology and psychiatry, 3 Ed., 1920, Lea and Febiger, Philadelphia, p. 637.

Pernicious Anemia without Achlorhydria*†

Case Report

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CHANGES in the stomach or in its secretions have been noted as a common finding in pernicious anemia for many years. As early as 1860 Austin Flint¹ spoke of an absence of gastric secretion and mentioned degenerative changes in the gastric mucosa. In 1877 Fenwick² noted atrophy of the gastric mucous membrane. Achlorhydria was spoken of by Cahn and von Mering³ as early as 1886 and again by von Noorden⁴ in 1891. Since these early reports, the absence of free hydrochloric acid from the gastric juice and a low total or combined acidity has usually been considered to be a typical or even a constant finding in this disease.

Achlorhydria has been known to exist in some cases for years before clinical symptoms of the disease developed. Ivy, Morgan and Farrell⁵ cite records from 18 different authors totaling 36 such cases. Strandell⁶ cites 23 cases reported by 13 different authors. The achlorhydria is usually considered to be a permanent condition in this disease even after a good remission has been brought about with

liver treatment. Minot and Murphy⁷ have reported it present in 18 patients when gastric analysis was performed from two to twenty-two months after a remission had been produced with liver therapy. Brauch⁸ reported achylia to be present in five cases in remission after treatment with liver. Strandell⁹ found achylia still present in one patient after a remission in the disease of sixteen and one-half years' duration without liver treatment. Shaw¹⁰ and Heeres¹¹ each report the return of hydrochloric acid with improvement in the anemic condition in one case not treated with liver.

Many of the earlier reports of gastric analyses made in patients considered to have pernicious anemia show a fairly large number with free hydrochloric acid present in the gastric contents. Stockton¹² found that three out of nine patients examined had free acid. Friedenwald and Morrison¹³ reported that 14 of 76 cases examined had free acid present but found it diminished in all except four patients in whom the gastric juice was normal.

Later reports, however, have only rarely recorded a patient without achlorhydria, perhaps because of the introduction of better methods of diagnosis. Cabot¹⁴ reported only one of

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†From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

79 cases of pernicious anemia tested; Percy¹⁵ found only one such case of those tested in his series of 129 cases (he does not state the number tested); Levine and Ladd,¹⁶ in reviewing the histories of 150 cases of pernicious anemia, reported only one patient with an unquestioned diagnosis out of 107 cases tested, in whom free hydrochloric acid was found to be present. In the cases which showed no free acid, 14 had a total acidity between 20° and 30°, seven between 30° and 40°, and two between 60° and 70°. Carr¹⁷ reported tests in 53 patients, in three of whom small amounts of free acid were found. Panton, Maitland-Jones and Riddoch¹⁸ reported that two of 35 cases tested had small amount of free acid; Willson and Evans¹⁹ found achlorhydria in all of 111 cases tested, and Grinker²⁰ found hydrochloric acid present in three of 74 cases tested. Pincy²¹ reported one case of subacute combined degeneration of the spinal cord in which free acid was present in the gastric secretion. No anemia was present, but viscosimetry showed the average volume of the red blood cells to be high and the diagnosis of pernicious anemia was later confirmed by history and by autopsy. Taubmann²² reported a typical case of pernicious anemia with free hydrochloric acid in the gastric juice. A remission of the disease occurred and the patient was discharged from the hospital with a red blood cell count of four million per cubic millimeter and a hemoglobin level of 93 per cent, although liver therapy was not used. One year later he reentered the hospital acutely ill and died. The cause of death was not known, although Minkowski²³ states

that it was probably not because of anemia. An autopsy was not performed.

The evidence as presented in the literature indicates that a disease condition typical of pernicious anemia in all essential respects, except that free hydrochloric acid is present in the gastric secretion, may occur. That such cases do occur is strong evidence against the etiological importance of achlorhydria in pernicious anemia. The work of Castle, Townsend and Heath²⁴ supplies further evidence to substantiate this idea. These same authors have also presented evidence of an alteration in the gastric contents which is more uniformly present than is achlorhydria and which they consider to be of greater etiological significance.

Because there is a paucity of reports of undoubted cases of pernicious anemia with free hydrochloric acid in the gastric contents, it seemed advisable to report the following case, giving the laboratory and clinical findings in considerable detail. The diagnosis is made more certain and the report more interesting by the typical, prompt and striking improvement in the blood following the institution of peroral liver therapy and again following the use of intramuscular injections of liver extract.

CASE REPORT

L.J.R., a 55-year-old, American-born housewife, entered the Peter Bent Brigham Hospital for the first time on July 15, 1930, complaining of jaundice, weakness and loss of weight.

Her illness dated from about February of the same year with the insidious onset of weakness, ease of fatigue, and loss of appetite. The weakness had steadily in-

creased and was accompanied by marked shortness of breath and forceful palpitation of the heart on moderate exertion. There followed subsequently swelling of the ankles, chilly sensations and anorexia, with nausea and vomiting at the sight of food, icterus, and the appearance of clay-colored stools. For a month before the present admission the patient had been troubled with dizzy spells and with a staggering gait. The fingers, feet and legs had felt numb and were often painful to pressure. Black and blue spots became evident following slight bruising. A persistently sore tongue developed. On June 5, 1930, she was seen in another Boston clinic at which time the following observations were made. The gastric contents showed free hydrochloric acid, the urine a slight trace of albumin with numerous white blood cells in the sediment. The blood showed a non-protein-nitrogen value of 25 milligrams per 100 c.c., a negative Wassermann reaction, 5.3 milligrams of bilirubin by the Van den Bergh test, 9.1 gm. of hemoglobin per 100 c.c., of blood, a red blood cell count of 1,680,000, and 3,800 white blood cells per cubic millimeter. Roentgen-ray studies of the gastrointestinal tract were interpreted as showing either a large diverticulum of the duodenum or a partial obstruction of the duodenum with dilatation. Intravenous cholecystograms showed no filling of the gall-bladder.

Thereafter until admission to this hospital the jaundice fluctuated in intensity and the weakness progressed.

The family history was irrelevant. The patient's first husband had died with pulmonary tuberculosis. Her second husband was living and well. The patient had always been strong, and except for the diseases of childhood and one cold each year, had suffered no ill health. The menstrual history was not unusual. There had been occasional slight bleeding from hemorrhoids. Nocturia, four to five times per night, had been present for many years. In 1925 a Bartholin's cyst had been removed; in 1927 an operation was performed for repair of the perineum and suspension of the uterus; and in 1929 another operation was done for repair of a postoperative ventral hernia and for bilateral inguinal herniae. Her nor-

mal weight was 175 pounds, but had decreased by about 25 pounds during the five months preceding the present hospital admission. A detailed dietary history failed to reveal evidence of a food deficiency.

Physical examination showed a large, well-developed woman lying comfortably in bed. She was mentally clear and coöperative. There was evidence of recent loss of weight. The hair was black with some graying and was normal in amount and texture. The skin showed a uniform brownish-yellow tint with several faint purpuric spots over the body. The pupils were equal, regular, and reacted normally to light and in accommodation. The sclerae were icteric. Ophthalmoscopic examination showed the optic discs to be normal in appearance. The left retina showed a small hemorrhage in the upper temporal quadrant and the right showed a small hemorrhage at the temporal side of the disc. The retinae were both pale but showed no areas of exudate. The retinal vessels appeared slightly larger than normal but showed no nicking, embedding, or tortuosity. The hearing was good. The mucous membranes of the mouth were pale and the teeth were all extracted. The tongue was smooth, clean, pale and slightly atrophic in appearance. It protruded in the midline without tremor. There were no areas of redness or of ulceration. There were loose folds of skin about the neck which suggested recent loss of weight. The thyroid gland was not palpable. The thorax was symmetrical and of normal appearance. Expansion was good and equal on both sides. Respirations were 20 per minute and of normal depth and character. The breasts were markedly atrophic. The heart was not enlarged. On auscultation a soft blowing systolic murmur was heard over the apex region. Examination of the heart was otherwise negative. The radial pulses were equal, and regular with a rate of 88 per minute. Palpation of the arterial vessel walls did not suggest sclerosis. There were many small prominent superficial veins below the knee and down the thigh. The blood pressure was 115 mm. of mercury systolic and 60 diastolic. The lungs were resonant throughout to percussion and tactile fremitus was normal. The voice and breath

sounds were normal and no râles were heard. The abdomen showed two midline scars. There was a small reducible right inguinal hernia. The abdominal reflexes were active. The lower edge of the liver was easily palpable three fingers' breadth beneath the costal margin. The gall-bladder, spleen, kidneys and bladder could not be felt. Rectal examination revealed small internal hemorrhoids on the left posterior wall, but none externally. Vaginal examination showed a slight cystocele. The cervix had a slight transverse laceration and the fundus of the uterus could not be felt. No adnexae felt. There was no enlargement of cervical, axillary, inguinal or epitrochlear glands. There was marked pallor of the fingers and nail beds. Dorsa of the wrists were heavily freckled. The biceps, triceps and radial-periosteal reflexes were equal and normal. No joint changes were noted. There was slight edema along the ankles and legs as high as the knee. There was a suggestion of positive Babinski and Oppenheim tests.

The knee jerks and Achilles reflexes were normal. The Romberg and Kernig tests were negative. There was paresthesia of the fingers of both hands. Vibration sense was decreased over the bony prominences of the arms and legs.

Clinical Laboratory Tests on Admission. The hemoglobin varied between 5.6 and 5.4 grams per 100 cubic centimeters. The red blood cells varied between 886,000 and 1,400,000 per cubic millimeter of blood as counted by various observers. They showed anisocytosis, poikilocytosis, and rare nucleated forms. There was a moderate number of macrocytes and microcytes. Slight polychromatophilia was noted. Hematocrit determination showed 16.2 per cent cells and 83.8 per cent plasma. The individual cell volume was 13.5 by 10^{-11} cubic centimeters. The average mean diameter of the red blood cells by the method of Price-Jones was 8.7μ . The fragility of the red blood cells was tested on two occasions and found to be within normal limits.

TABLE I
BLOOD EXAMINATIONS

Date	Hb. in grams 100 c.c.	R.B.C. in millions	W.B.C.	Differential P-L-M-E-B	Reticulo- cytes in percentage	I.C.V.* (10^{11} c.c.)	Icteric index	Blood iron per 100 c.c.
June 5, 1930	9.1	1.68	3,800					
June 15, 1930	5.6	1.40	3,500				15	
June 17, 1930	5.6	.88				18.2	25	
June 22, 1930	5.4	1.20	4,800	60-35-5-0-0	1.2	13.5		
June 25, 1930		.89					25	
June 25, 1930		1.03		60-31-5-4-0	0.8			
June 30, 1930		1.32		42-50-5-3-0	1.8			
June 31, 1930		1.08			8.8			
Aug. 1, 1930		1.02			13.5			
Aug. 2, 1930		1.32			16.4			
Aug. 3, 1930		1.29			19.3			
Aug. 4, 1930		1.60			16.2			
Aug. 5, 1930		1.56		55-39-3-2-1	13.8			
Aug. 6, 1930					3.8			
Aug. 7, 1930		1.90	4,700		2.5			
Aug. 8, 1930		1.52			1.9			
Aug. 9, 1930	6.1	1.93			1.5			
Aug. 11, 1930		1.78					12	24.25
Aug. 13, 1930	6.6	1.71				12.3		
Aug. 15, 1930		2.22						
Aug. 19, 1930	8.4	2.83						
Aug. 26, 1930	8.4	3.04				11.5	8	

TABLE I—(Continued)

Date	Hb. in grams 100 c.c.	R.B.C. in millions	W.B.C.	Differential P-L-M-E-B	Reticulo- cytes in percentage	I.C.V.* (10 ¹¹ c.c.)	Icteric index	Blood iron per 100 c.c.
Sept. 2, 1930	8.3	3.28						
Sept. 9, 1930	11.3	3.50	5,000					
Sept. 16, 1930	11.3	3.10						
Sept. 27, 1930	11.2	3.16				12.0		41.3
Oct. 4, 1930	12.6	4.23						
Oct. 11, 1930	12.7	4.01	5,500					
Oct. 18, 1930	13.6	3.66						
Oct. 25, 1930	13.6	3.66	4,250			10.4		40.0
Nov. 1, 1930	13.3	4.18						
Nov. 8, 1930	12.7	4.25						
Nov. 15, 1930	13.4	4.09						
Nov. 22, 1930	12.6	3.81						
Nov. 29, 1930	13.0	4.19						
Dec. 10, 1930	11.9	3.24	8,150					
Dec. 18, 1930	12.4	3.23						
Dec. 27, 1930	12.2	3.34						
Jan. 8, 1931	13.4	3.87	5,700	64-28-4-4-0		9.7		40.0
Jan. 14, 1931	12.7	4.08	7,300	57-36-4-2-1				
Jan. 22, 1931	10.5	2.93			2.2			
Jan. 23, 1931					3.5			
Jan. 24, 1931					4.2			
Jan. 26, 1931					3.3			
Jan. 27, 1931	13.7	3.84			2.4			
Feb. 3, 1931	13.7	4.37						
Feb. 7, 1931	14.4	4.68						
Feb. 21, 1931	13.4	3.56				10.2		40.16
Mar. 13, 1931	12.7	3.46	6,800					
Mar. 21, 1931	13.32	3.59						
May 19, 1931	7.8	1.82	2,750	36-60-4-0-0	1.1			
May 20, 1931					0.8			
May 21, 1931					3.5			
May 22, 1931			3,750		10.7			
May 23, 1931	8.1	2.17			13.5			
May 25, 1931	8.4	2.16			13.7			
May 26, 1931					12.4			
May 27, 1931					9.0			
May 28, 1931					10.1			
May 29, 1931					8.5			
May 30, 1931			4,500					
June 2, 1931					7.2			
June 5, 1931	9.5	3.00	5,200	60-37-3-0-0	1.2			
June 10, 1931	10.1	3.87			1.8			
June 12, 1931			6,000	64-34-2-0-0				
June 17, 1931	11.1	3.15	9,550	88-10-2-0-0				
June 20, 1931			16,100					
June 25, 1931	10.3	3.80	28,000					

*I.C.V. = Individual cell volume.

TABLE II

July 15, 1930	Bleeding and clotting time normal.
July 25, 1930	Van den Bergh—Delayed direct reaction. Quantitative 4.8 V.d.B. units or 2.4 mg. bilirubin per 100 c.c.

BLOOD CHEMISTRY

JANUARY 8, 1931		FEBRUARY 21, 1931	
Blood urea nitrogen.....	11.2	Blood urea nitrogen.....	18.2
Non-protein-nitrogen	33.7	Non-protein-nitrogen	28.9
Amino acid nitrogen.....	9.61	Amino acid nitrogen.....	7.43
Uric acid.....	2.15	Uric acid.....	2.81
Blood sugar.....	0.121	Blood sugar.....	0.105
Total protein.....	6.33	Total protein.....	5.71
Albumin	4.96	Albumin	3.84
Globulin	1.01	Globulin	1.12
Fibrinogen	0.36	Fibrinogen	0.75
Total creatinine.....	5.16	Total creatinine.....	8.22
Preformed creatinine.....	1.43	Preformed creatinine.....	2.60
Cholesterol	143.0	Cholesterol	113.6
Blood iron.....	40.0	Blood iron.....	40.16

There was a definite leukopenia, the white blood cells varying from 3,500 to 4,800 per cubic millimeter. The differential white blood cell count was essentially normal except that the polymorphonuclear leukocytes showed characteristic hypersegmentation of the nuclei and the Arneth count showed a marked shift to the right with an Arneth index of fifteen.

Both the bleeding and the clotting time were normal. The icteric index was 15 and 25 on successive determinations. The Van den Bergh test gave a delayed direct reaction. Quantitative determination gave 4.8 Van den Bergh units or 2.4 milligrams of bilirubin per 100 cubic centimeters. Wassermann, Hinton, and modified Hinton tests were negative.

Gastric analysis done on several occasions showed the presence of adequate amounts of free hydrochloric acid as well as of pepsin and rennin. (See table 3*)

The basal metabolic rate was plus six. The electrocardiogram showed normal curves.

Urine studies were essentially negative. The test for Bence-Jones protein was nega-

tive. Phenolsulphonephthalein excretion was 32 per cent in two hours and ten minutes.

Stool studies did not reveal abnormalities. Careful search was made for ova and parasites.

Temperature, pulse and respirations were within normal limits on admission and remained within these limits during all periods except that preceding death.

Cholecystograms (intravenous) failed to show a normal gall-bladder shadow at ten, twelve and fourteen hours. The findings indicated a pathological gall-bladder.

The esophagus appeared normal by roentgen-ray examination. The stomach was low and hypotonic, showed vigorous peristalsis, a smooth outline, and no residue at six hours. The duodenal cap was large, and filled and emptied well. There was a large diverticulum in the second portion of the duodenum, and two other diverticuli at the duodeno-jejunal junction. There were also multiple diverticuli in the small bowel distal to this. Hypomotility was present, barium not having filled the cecum at six hours. The twenty-four hour examination showed a long atonic redundant colon. The cecum was fixed in the pelvis and the ascending colon was medial to the usual position. The diverticuli noted on the previous day were

*A more complete record of the results of observations of the blood may be seen in tables I and 2

empty. The roentgenological impression was diverticulosis.

Films of the long bones showed an irregular thickening of the cortex of the left fibula and a lesser amount of thickening on the right. The bones all appeared slightly

a day. Vomiting ceased. Following this therapy she had a typical and fairly satisfactory reticulocyte response reaching a peak of 19.3 per cent on the tenth day after starting liver therapy. The reticulocyte response is shown on chart 1.

TABLE III
GASTRIC ANALYSIS

	Residue	Benzidene	Reaction	Free HCl	Total Acid	Rennin
Fasting spec., 13 c.c. pinkish mucoid fluid	1%	Negative	Neutral	0	6	1- 320
EWALD MEAL*:						
1st specimen: 7 c.c. bready grey fluid	3%	Positive	Acid	60	75	1- 640
2nd specimen: 9 c.c. bready greenish fluid	3%	"	"	6	10	1- 640
3rd specimen: 14 c.c. bready pale yellow fluid	2%	"	"	0	24	1- 640
4th specimen: 17 c.c. bready amber fluid	2%	"	"	0	10	1- 160
HISTAMINE†: 0.5 mg. intramuscularly						
5th specimen: 17 c.c. bready green fluid	2%	"	"	35	51	1-1280
6th specimen: 14 c.c. cloudy green fluid	2%	"	"	52	86	1-1280
7th specimen: 30 c.c. cloudy green fluid	2%	"	"	77	96	1-2560
8th specimen: 15 c.c. hazy green fluid	2%	"	"	73	82	1-2560

*The Ewald meal consisted of 60 gms. of bread and 200 c.c. water. The first and second specimens were obtained at twenty-minute intervals, the third and fourth at forty-minute intervals.

†Histamine was given intramuscularly and specimens obtained every fifteen minutes. Difficulty was experienced in obtaining second, third and fourth specimens so that 10 c.c. of water was introduced into the stomach through Rehfuess tube and washed back and forth through tube. This procedure undoubtedly accounts for the low figures obtained in titrating specimens against tenth-normal sodium hydroxide. Pepsin was positive in all specimens as determined by the ordinary test with Mett's tube in dilute hydrochloric acid. Rennin was positive in all specimens in dilutions noted in table. This analysis was done on January 7, 1931. Gastric analyses were done on four other widely separated occasions and agreed with the essential findings noted above. The slightly positive benzidene tests are accounted for by trauma to the gastric mucosa.

decalcified. No localized areas of bone destruction were seen, except possibly on the styloid process of the right ulna where the bone appeared somewhat thinner than usual.

Progress Notes. On July 24 the patient began the ingestion of 240 grams of raw liver pulp daily. (See table 4 for complete record of treatments.) Much of the liver pulp was vomited, and on July 27 the liver pulp was discontinued and she was given daily liver extract No. 343 (N.N.R.), the amount derived from 800 grams of liver. This was well taken with the addition of twelve minims of tincture of belladonna three times

During the patient's stay in the hospital she continued to make excellent clinical improvement. The red blood cell count increased from about one million at the time of admission to two million on August 16, 1930, twenty-one days after liver extract therapy was begun. The patient continued to take daily liver extract prepared from 800 grams of liver. She was then discharged from the hospital and seen at weekly intervals, the blood showing continued, gradual improvement until the hemoglobin was 12.6 grams per 100 cubic centimeters and the red blood cells 4,230,000

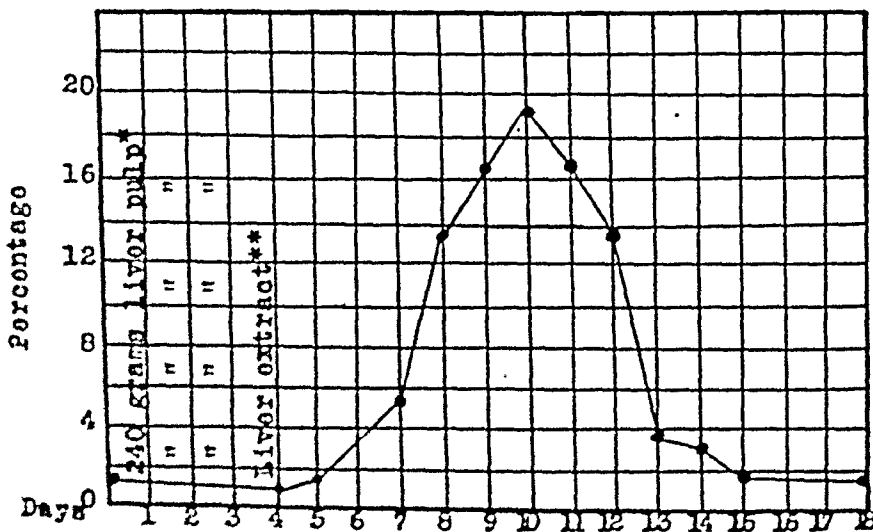
per cubic millimeter on October 4, 1930. For the next two months the blood picture remained about constant. The following month there was a definite fall in the red blood cell count and hemoglobin, although she had taken extract prepared from 400

to 600 grams of liver daily. During the six months following discharge from the hospital the neurological signs became progressively more marked. The patient staggered while walking. The numbness and tingling in the hands and feet seemed on the

TABLE IV

1930	
July 24 to July 27.....	Liver pulp 240 grams daily. (Partially taken.)
July 27 to Sept. 2.....	8 vials liver extract No. 343 (N.N.R.) daily.
Sept. 2 to Sept. 27.....	6 vials liver extract No. 343 (N.N.R.) daily.
Sept. 27 to Oct. 11.....	4 vials liver extract No. 343 (N.N.R.) daily, plus one pound of liver a week.
Oct. 11 to Nov. 8.....	8 vials liver extract No. 343 (N.N.R.) daily, plus one to one and a half pounds liver a week.
Nov. 8 to Nov. 20.....	6 vials liver extract No. 343 (N.N.R.) daily.
Nov. 29 to Jan. 7.....	4 vials liver extract No. 343 (N.N.R.) daily.
1931	
Jan. 7 to Jan. 17.....	8 vials liver extract No. 343 (N.N.R.) daily.
Jan. 17 to Jan. 20.....	Recovering from operation.
Jan. 20 to Feb. 21.....	8 vials liver extract No. 343 (N.N.R.) daily.
Feb. 21 to Mar. 13.....	6 vials liver extract No. 343 (N.N.R.) daily.
Mar. 13 to May 19.....	6 vials liver extract No. 343 (N.N.R.), plus one-fourth of a pound of raw liver daily.
May 19.....	15 c.c. intramuscularly aqueous solution of liver extract prepared from 200 gm. of liver.
May 20.....	10 c.c. intramuscularly aqueous solution of liver extract prepared from 150 gm. of liver.
May 21 to June 28 inc....	daily intramuscular injection of 2 c.c. aqueous solution of liver extract prepared from 10 gm. of liver.

CHART I
RETICULOCYTE RESPONSE FOLLOWING LIVER THERAPY.



*Partially vomited and refused.

**Prepared from 800 grams of raw liver. Given daily.

whole to become more severe and constant in spite of the improvement in the blood picture. She complained bitterly of coldness and stiffness of the extremities. The fingers were clumsy so that she was unable to put on gloves without assistance.

The patient's failure to make complete recovery was thought to be partly due to the gall-bladder disease that had been suspected during her first admission to the hospital. She entered the medical service for the second time. Intravenous cholecystograms were repeated and failed to show a gall-bladder shadow. Cholecystectomy was advised and the patient was transferred to the surgical service. On January 17, 1931,* under avertin and ether anesthesia, the gall-bladder was removed in the usual manner. The liver was involved in a diffuse perihepatitis. The pathological specimen showed a gall-bladder 15 centimeters in length and 6 centimeters in diameter. The surface was smooth except where it had been detached from its bed. On opening the gall-bladder a considerable quantity of poorly concentrated bile escaped. There was a solitary stone measuring 3.8 by 2.8 by 2 centimeters. This had a rusty color and a slightly roughened surface. Within the gall-bladder was a small amount of scaly material of about the same color. The mucosa was not injected and of quite normal appearance. A few strands of fibrous tissue were seen in some areas but these were not prominent. Microscopic section of the gall-bladder showed moderate fibrosis with chronic inflammation. Culture of the bile and wall of the gall-bladder showed no growth. The pathological diagnosis was chronic cholecystitis and cholelithiasis. The patient made an uneventful postoperative recovery except for slight vomiting on the first and second days. Following the operation the hemoglobin dropped to 10.5 grams per 100 cubic centimeters of blood and the red blood cells to 2,930,000 per cubic millimeter. Liver extract was given and there was a slight reticulocyte rise reaching a peak of 4.2 per cent on the sixth day following

operation (see table 1). A rapid recovery in the blood picture was noted (see chart 2) reaching a peak on February 7, 1931. The patient was still weak and unable to walk alone. She was discharged with instructions to continue to take daily the liver extract prepared from 800 gm. of liver. On February 9, 1931, she became quite constipated and developed an attack of vomiting which lasted about twenty-four hours. She returned to the hospital for observation on February 21, 1931, at which time her blood showed 13.4 grams of hemoglobin per 100 cubic centimeters of blood and 3,560,000 red blood cells per cubic millimeter. There was little or no change in the chemical tests of the blood. The Arneth count showed a shift toward normal with an index of 40. She was weak and unable to walk. She was advised to continue to take daily liver extract prepared from 600 gm. of liver. On March 13, 1931, there were 12.7 grams of hemoglobin per 100 cubic centimeters of blood and 3,460,000 red blood cells per cubic millimeter. On several occasions she was troubled with a slight diarrhea. On the whole her general condition grew gradually worse after leaving the hospital. The neurological symptoms showed little or no improvement, although she was able to walk with assistance. The blood picture was not satisfactory but showed some improvement so that the red and white blood cells appeared more normal.

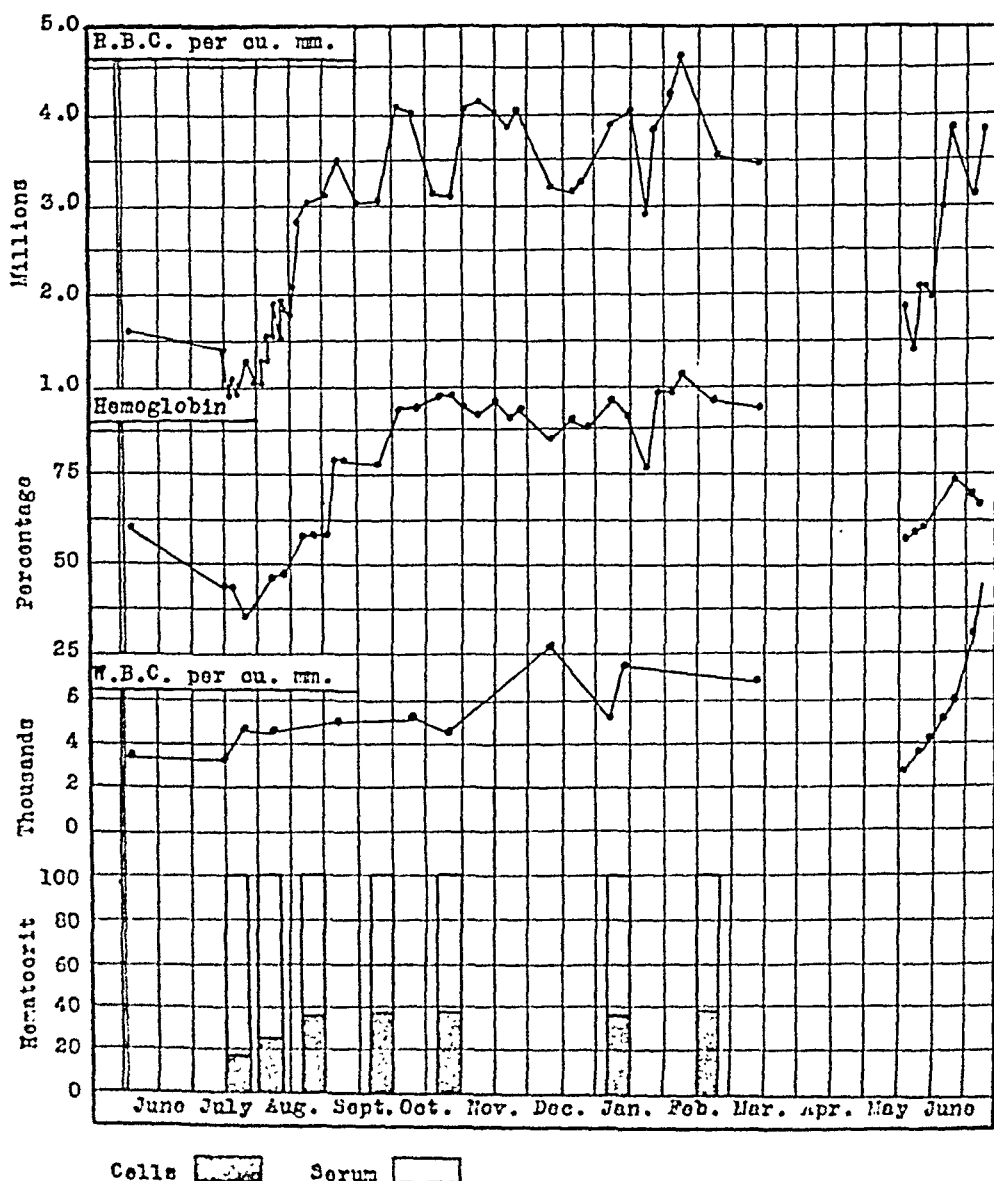
During the months of March and April her health continued to fail. There was progressive weakness in the legs. The numbness and tingling involved both upper and lower extremities and was constant. There was edema of both legs. Her appetite failed. She was troubled much with diarrhea and reported that the liver extract passed through the bowel unchanged. On occasions there was a sensation as though the abdomen were being distended with gas. In May 1931, she was unable to walk without assistance and finally was confined to bed. She developed mental changes, becoming more irritable and having periods during which she would scream almost constantly. On May 17, 1931, she was seen by one of us (W.P.M.), who found the blood pressure 86 mm. of mercury systolic

*Operation was performed by Dr. John Homans of the surgical staff of the Peter Bent Brigham Hospital.

and 55 diastolic. The heart sounds were barely audible and the pulse weak. There was marked edema of the extremities and definite icterus. She was incontinent and unable to move the lower extremities. A

tests were poorly executed. There was definite impaired pain, temperature, vibratory, tactile and position sense in the legs. The reflexes were increased in both arms and markedly exaggerated in both legs. An

CHART II



Observations on Hemoglobin, R.B.C., W.B.Cs. & Hematocrit

trophic ulcer was present over the lower back.

She entered the hospital for the third time on May 19, 1931. Physical examination showed the sclerae slightly icteric and the mucous membrane pale. The arms and legs were spastic. Hands and fingers were clumsy. Finger to nose, and heel to knee

unsustained patellar and ankle clonus was present. Positive bilateral Babinski and Oppenheim tests were observed with brief patellar and ankle clonus. The hemoglobin was 7.7 grams per 100 c.c. of blood with 1,820,000 red blood cells per cubic millimeter. Intramuscular liver extract was given with a definite reticulocyte response

reaching a peak of 13.7 per cent on the sixth day of treatment.²⁵ The red blood cell count increased approximately two million in the following month. Although the blood made a definite response, the trophic ulcer gradually enlarged in size and depth. A rise in temperature occurred with leukocytosis; she gradually became weaker and died on June 28, 1931.

POSTMORTEM EXAMINATION

A complete necropsy was performed four hours after death on a white woman who was well developed but poorly nourished. She appeared older than her stated age of 56 years. The hair was black, streaked with grey and of normal texture. The eyes were blue, the pupils were unequal, the right measuring 4 mm. and the left 3 mm. in their respective diameters. The left pupil was irregular and eccentrically placed, being above the center of the iris. A decubitus ulcer measuring 8 by 14 cm. in diameter and extending down to the bone was found over the right and left trochanters. Further exploration of the ulceration in the region of the right trochanter revealed a cellulitis extending between the gluteal muscles to the sacrum. The ulceration over the left trochanter was continuous with a cellulitis which extended down the thigh to the prepatellar bursa and also involved this structure. The muscles underlying the needle puncture marks in the left gluteal region showed no evidence of inflammation. On the right side the muscles were involved in the inflammatory process already described. There was marked edema of the left foot and leg. The left femoral and iliac veins were filled by a laminated thrombus. The subcutaneous fat which remained was of a lemon yellow color. The pectoral muscles were atrophied.

The pathological changes in the heart, lungs, spleen, intestines, adrenals and genitourinary organs were irrelevant to her anemic condition other than for a slight fatty degeneration of the heart muscle seen in the interventricular septum and columnae carneae.

The liver weighed 2260 grams, was of a pale yellow-brown color with prominent liver markings. It was softer in consistency

than normal and very fragile. The former gall-bladder bed was well healed.

The pancreas was of normal color and size but was slightly softer than usual.

The stomach was of average size, had a fairly well preserved mucosa which was thrown into the usual folds. The mucosa showed no evidence of atrophy, ulceration, or tumor.

The entire marrow, exposed from the middle of the shaft of the femur to the articular end was of a deep red color and none of the fatty marrow usually seen was apparent.

The cord was of normal size and the meninges were free from exudate. Cross sections of the cord at the time of the post mortem showed no changes which were recognized on gross inspection. The superior longitudinal and the right lateral sinus contained an antemortem thrombus. The meninges were free from exudate. Morbid changes of the brain were found neither before nor after fixation.

The culture made of heart's blood taken from the right auricle contained *Staphylococcus aureus hemolyticus*.

Microscopic Examination. The minor pathological changes which were found in the heart, lungs, kidneys, spleen, adrenal glands, aorta and brain were irrelevant to the anemic condition.

The sections taken from the fundic, cardiac and pyloric areas of the stomach showed a mucosa of average width for these respective areas. The parietal cells were present in large numbers and were well preserved. The sections from the pylorus contained the usual deep mucus-secreting glands. There was no atrophy, ulceration of the mucosa, or evidence of a malignant new growth.

The section of muscle fibers taken from the left gluteal region at the site of liver extract injection showed atrophy but there was no inflammatory reaction and no cellular infiltration.

The liver showed a marked periportal fatty infiltration.

The pancreas showed a replacement of some of the acinar structures by fat cells.

The sections of bone marrow taken from the femur showed a marked replacement of

the fatty marrow by a highly cellular tissue. Many of these cells were identified as belonging to the granulocytic series, although lymphocytes and plasma cells were fairly numerous. There were also immature cells which could not be definitely identified. Mature and immature eosinophiles were numerous among the granulocytic cells. Occasionally a basophile was seen. Megakaryocytes, frequently of small size, were scattered throughout. Scattered among the granulocytic and immature cells were clusters of cells representing erythropoietic centers, most of the cells of which were well differentiated and not of the undifferentiated megaloblastic type seen in pernicious anemia. Occasionally a small amount of brownish pigment was present but nowhere was it abundant. The blood vessels throughout were engorged. The histology of the marrow was consistent with what is seen in the remission period in pernicious anemia or following the response to liver therapy.

Sections were taken from the cervical, dorsal, and lumbar regions of the spinal cord. They all showed marked degeneration of the nerve fibers without extensive cellular reaction or gliosis. The areas of degeneration were not sharply outlined but corresponded with the areas ascribed to the following nerve fascicles, gracilis, cuneatus, dorsal and ventral spinocerebellar, posterior spinothalamic and spinotectal, lateral cerebrospinal and rubrospinal. There was no apparent degeneration of the grey matter of the cord and the ganglion cells were well preserved. There was no inflammatory reaction in the pia arachnoid or dura. The ganglion cells of two dorsal root ganglia were well preserved.

Dr. Schulz' summary of the findings follows.*

The postmortem examination revealed extensive ulcerations of the sacrum with an extension of the cellulitis to the hip, thigh, and prepatellar bursa. Death, at least in part, was due to this condition. The thrombophlebitis and the thrombosis of the superior and lateral sinuses were additional important factors in the causation of death.

*We are indebted to Dr. R. Z. Schulz for permission to record his summary of the postmortem findings.

The anemic condition was rather puzzling. Such possible causes as malignant tumors of epithelial origin, particularly carcinoma of the stomach, sarcomatous tumors and leukemia, could all be ruled out.

The cord changes were those found in pernicious anemia, and these changes may be considered a positive factor in favor of the diagnosis of pernicious anemia. The hyperplastic red blood elements in the bone marrow were of a character consistent with a spontaneous or induced remission in this disease. The absence of another etiological factor to account for the anemia was also circumstantial evidence favoring the diagnosis. The blood changes observed on clinical examination and the response of these to intramuscular liver therapy were characteristic of pernicious anemia.

On the other hand the stomach showed none of the atrophy usually found in pernicious anemia; the acid-secreting cells were numerous and well preserved and the other glandular elements showed no degeneration or atrophy. These findings, together with the presence of free hydrochloric acid reported clinically, constituted the chief factors which were not characteristic of pernicious anemia.

There have, however, been a number of cases of pernicious anemia reported in which hydrochloric acid was present in the stomach and others in which it was absent but reappeared to a slight extent after treatment. The poor response to oral administration of liver extract in this case may have been due to the presence of free hydrochloric acid as suggested by Dr. Christian. Since the etiology of pernicious anemia is at present disputed and since the disease is diagnosed by a combination of symptoms together with the exclusion of known causes of anemia, it is our opinion that this case should be classed with the group of pernicious anemia. Whether it is one of the closely allied conditions cannot be ruled out from the postmortem findings. We, therefore, are recording it under the diagnosis of pernicious anemia.

COMMENT

The case presented is that of a patient with a blood picture and symptoms entirely compatible with a diag-

nosis of pernicious anemia, but with free hydrochloric acid, as well as rennin and pepsin in the gastric contents. A response of the reticulocytes and red blood cells occurred as the result of the ingestion of liver extract similar to that which would be expected in a case of pernicious anemia complicated by disease of the gall-bladder. Subsequently a relapse occurred during a period in which a rather large amount of liver extract was being ingested although, owing to a severe diarrhea, it was probably not being absorbed for use in the formation of blood cells. Dr. Christian has suggested a possible destructive action of the hydrochloric acid of the stomach on the active substance in liver extract. The blood, however, again improved following the intramuscular injection of a liver extract. There is undoubtedly evidence in this case of the retarding influence of complicating factors (gall-bladder disease with liver damage, diverticulo-

sis and diarrhea) in the subnormal response of the reticulocytes to liver therapy, the incomplete response of the red blood cells to a rather large intake of liver extract, and the unsatisfactory course of the disease. Of what etiological significance these same complications are is a matter for speculation.

The possible importance of disease of the gall-bladder or liver in the occurrence of pernicious anemia has been suggested by several observers, notably Lord Dawson of Penn.,²⁶ Harris,²⁷ Jones²⁸ and others. Although Castle and his co-workers have demonstrated the absence in the gastric secretions in pernicious anemia of a substance or function which is present in the normal stomach it would seem possible in view of the inconstancy of the achlorhydria that the disturbances in the biliary system or liver may sometimes be of even more immediate etiological importance than are the gastric changes.

BIBLIOGRAPHY

- ¹FLINT, A.: A practical treatise on the diagnosis, pathology and treatment of diseases of the heart, N. Y. Med. Jr., 1860, viii, 267.
- ²FENWICK, S.: Lecture on atrophy of the stomach, Lancet, 1877, ii, 1-4, 39-41, 77-78.
- ³CAHN, A., and VON MERING, J.: Die Säuren des gesunden und kranken Magens, Deutsch. Arch. f. klin. Med., 1886, xxxix, 233-253.
- ⁴VON NOORDEN, C.: Untersuchungen über schwere Anämien (Blut, Stoffwechsel Nervensystem), Charité-Ann., 1891, xvi, 217-266.
- ⁵IVY, A. C., MORGAN, J. E., and FARRELL, J. I.: The effects of total gastrectomy; experimental achylia gastrica in dogs with the occurrence of a spontaneous anemia and anemia in pregnancy, Surg., Gynec. and Obst., 1931, liii, 611-620.
- ⁶STRANDELL, B.: Pernicious anemia; a study of 117 cases, Acta med. Scandinav., Supplementum 40, 1931.
- ⁷MINOT, G. R., and MURPHY, W. P.: A diet rich in liver in the treatment of pernicious anemia, study of 105 cases, Jr. Am. Med. Assoc., 1927, lxxxix, 759-766.
- ⁸BRAUCH, F.: Magenfunktionsprüfung an Fällen von perniziöser Anämie nach Lebertherapie, Fortschr. Ther., 1929, v, 412.
- ⁹STRANDELL, B.: A case of pernicious anemia, well sixteen and one-half years after diagnosis, Acta med. Scandinav., 1929, lxxii, 348-368.
- ¹⁰SHAW, M. E.: A case of apparent recovery from Addison's anemia and the associated achlorhydria, Guy's Hosp. Rep., 1926, lxxvi, 294-302.
- ¹¹HEERES, P. A.: Liver diet in pernicious

- anemia with return of free hydrochloric acid, *Nederlandsch Tijdschrift v. Geneeskunde*, Harlem, 1928, lxxii, 2325.
- ¹²STOCKTON, C. G.: Pernicious anemia and its relation to gastric digestion, based on twenty-five cases, *Jr. Am. Med. Assoc.*, 1904, xliii, 165-169.
 - ¹³FRIEDENWALD, J., and MORRISON, T. H.: Gastrointestinal disturbances in pernicious anemia, *Jr. Am. Med. Assoc.*, 1919, lxxiii, 407-410.
 - ¹⁴CABOT, R. C.: Pernicious anemia, in OSLER and MCCREA: *Modern medicine*, 1915, iv, 619.
 - ¹⁵PERCY, N. M.: Blood transfusion in association with other surgical procedures in the treatment of pernicious anemia, with report of cases, *Trans. Am. Surg. Assoc.*, 1920, xxxviii, 451-463.
 - ¹⁶LEVINE, S. A., and LADD, W. S.: Pernicious anemia; a clinical study of one hundred and fifty consecutive cases with special reference to gastric anacidity, *Johns Hopkins Hosp. Bull.*, 1921, xxxii, 254-266.
 - ¹⁷CARR, J. G.: Pernicious anemia; a study of one hundred and forty-eight cases, *Am. Jr. Med. Sci.*, 1920, clx, 737-752.
 - ¹⁸PANTON, P. N., MAITLAND-JONES, A. G., and RIDDOCH, G.: Pernicious anemia; an analysis of 117 cases, *Lancet*, 1923, i, 274-279.
 - ¹⁹WILLSON, C. R., and EVANS, F. A.: An analysis of the clinical histories of patients with pernicious anemia in the Johns Hopkins Hospital from 1918 to 1922 inclusive, *Johns Hopkins Hosp. Bull.*, 1924, xxxv, 38-46.
 - ²⁰GRINKER, R. R.: Pernicious anemia, achylia gastrica and combined cord degeneration and their relationship, *Arch. Int. Med.*, 1926, xxxviii, 292-302.
 - ²¹PINEY, A.: Pernicious anemia, *British Med. Jr.*, 1924, i, 271.
 - ²²TAUBMANN, G.: Perniziöse Anämie mit erhaltener Salzsäuresekretion, *Deutsch. Arch. f. klin. Med.*, 1926, cl, 309-314.
 - ²³MINKOWSKI, O.: Personal communication, Wiesbaden, Germany, November 1930.
 - ²⁴CASTLE, W. B., TOWNSEND, W. C., and HEATH, C. W.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia; nature of reaction between normal human gastric juice and beef muscle leading to clinical improvement and increased blood formation similar to effect of liver feeding, *Am. Jr. Med. Sci.*, 1930, clxxx, 305-335.
 - ²⁵MURPHY, W. P.: The parenteral use of liver extract in pernicious anemia, *Jr. Am. Med. Assoc.*, 1932, xcvi, 1051.
 - ²⁶LORD DAWSON OF PENN.: Pernicious anemia, *Lancet*, 1928, i, 115.
 - ²⁷HARRIS, S.: The liver diet and liver extracts in the treatment of pernicious anemia, *Internat. Clinics*, 1928, xi, 132.
 - ²⁸JONES, N. W., and JOYCE, T. M.: Further remarks on infection of gall-bladder in relation to chronic (pernicious?) anemia, *Am. Jr. Med. Sci.*, 1927, clxxiii, 526.

Standardization of Diabetics with Diet and Insulin*

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ONE hesitates to use the term "standardization" in relation to the treatment of disease. We rightly should consider each patient as an individual and adapt our treatment accordingly.

In the management of diabetes the term "standardization", however, is used to indicate two necessary steps in treatment. The first is the control of the disease, by which is meant the reduction of the blood sugar to normal levels, with or without insulin, with the patient on a maintenance diet. A diet containing a properly balanced proportion of carbohydrate, protein, and fat, and sufficient total calories to enable the patient to carry on his or her daily activities without loss of weight below a certain predetermined standard.

Of greater importance than the control of the disease is the second step which includes the proper education of these diabetics and their instruction in diet and hygiene, so that they are able properly to care for themselves at home. Unless this is done, the patient is discharged from the hospital faced with the choice of either eating the same meal day after day or of sitting

down to each meal in fear and confusion.

This is by far the most important step in the standardization of these patients, and unless they are satisfactorily educated the temporary control of the situation is valueless, and they return again and again in various stages of decompensation of the insulinogenic system until severe coma or some other preventable complication causes a fatal termination.

The diabetic who is taught diet calculation, a few simple laboratory examinations, and the importance of diabetic hygiene is able to adapt himself to his surroundings and to lead a normal type of life.

The use of a subnormal caloric diet, or the so-called "test diet", has largely been discarded because this involves frequent changes of diet and also of insulin which tend to confuse the patient. These individuals must be discharged on a diet which is adequate calorically for their daily needs. As this can usually be calculated accurately in advance, it is far better to place the patients on this as their initial diet and readjust the insulin dosage to care for it if necessary, rather than to waste time by gradually increasing the diet as the patient's tolerance warrants.

The term "diabetic diet" is a poor

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one and should be avoided as, with the exception of foods with a very high carbohydrate content, such as sugar, honey, candy, pastry and the like, there are really no foods that a diabetic may not include in his menu if proper allowance is made for the amount of carbohydrate, protein, and fat which they contain.

In constructing the diet of the diabetic there are certain fundamental facts which must be borne in mind.

First, it is generally agreed that the diabetic should have a lower caloric diet than his normal diet. It has been found that a diet which allows 30 calories per kilogram of body weight per day is satisfactory for patients engaged in ordinary occupation. In cases in which the patient must do hard physical labor it may be necessary to increase this to 40 or 45 calories per kilogram of body weight per day, but it has been our experience that these instances are rather infrequent.

Second, it has been shown that 0.7 to 1.0 gram of protein per kilogram of body weight per day is required to maintain a nitrogen balance and 1.0 gram per kilogram is a satisfactory allowance for the average diabetic.

Third, the carbohydrate and fat must be so adjusted that there will be sufficient carbohydrate to completely burn the fatty acid derived from the fat in order to avoid the danger of acidosis from the diet itself. This fortunately can be determined beforehand by the use of Woodyatt and Schaeffer's ketogenic and antiketogenic ratio.

There are three schools of thought in regard to the exact carbohydrate allowance. These are briefly:

(A). *The Low Carbohydrate and*

High Fat Diet. The advocates of this diet claim for it the advantage of requiring a lower insulin dosage. Its theoretical disadvantages are that it gives a very low margin of safety as far as the ketogenic and antiketogenic balance is concerned, and that it tends to produce a lipemia and subsequent arteriosclerosis. There is, moreover, the clinical disadvantage that a diet low in carbohydrate is not a very palatable one for the average person and so its use adds another temptation to break the routine.

(B). *The High Carbohydrate Diet.* In this diet, first advocated by Sansum and his co-workers, the patients are allowed 200 gm. and upward of carbohydrate a day. Indeed their carbohydrate allowance may differ but little from a so-called normal diet. Such a diet has the advantage of being palatable and easy to accommodate to the menu of the rest of the family. It also, by tending to do away with a lipemia, lessens the patient's chances of developing acidosis and arteriosclerosis. It has the distinct disadvantage that larger doses of insulin are required.

(C). *The Moderately High Carbohydrate Diet.* We have found this diet, which is advocated by Joslin and others, to be the most satisfactory. The formula which we have used in most of these cases is:

1½ to 2 grams of carbohydrate per kilogram of body weight per day. 1 gm. of protein per kilogram of body weight per day.

Fat qs. to make 30 calories per kilogram of body weight per day.

This allowance, of course, is based on ideal weight and for the average

individual means a daily allowance of over 100 gm. of carbohydrate per day. The figures given above are for cases in adults.

If, after three to five days on such

and caloric allowance per kilogram, because of the nutritional needs that go with bodily development. The following table¹ we have found useful as a guide in these cases:

TABLE I

Age	2	4	6	8	12
Carbohydrate (per kilogram of body weight per day)	10-12 gm.	7-9 gm.	4-6 gm.	3-5 gm.	2.5-3 gm.
Protein (per kilogram of body weight per day)	4.5 gm.	4 gm.	4 gm.	3 gm.	2.5 gm.
Calories (per kilogram of body weight per day)	90	80	75	65	55

a "maintenance diet", the blood sugar is still above normal, insulin is indicated.

It might not be amiss to consider at this point what a normal blood sugar value should be. It has been shown that elderly diabetics with sclerosis of the coronary arteries do not stand well attempts to depress the blood sugar level too low and frequently develop cardiac symptoms. A safe figure to take as "low normal" is one-half the patient's age plus 100 (expressed in milligrams per 100 c.c. of blood).

Many elderly diabetics past middle life do better if the fasting blood sugar is .014 or .015 per cent.

Diabetes in children is an acute disease. The onset is usually abrupt, the disease severe and the margin of safety between coma and hypoglycemia is small. To compensate for this, however, children seem to stand both coma and hypoglycemia better than adults and may recover promptly from a degree of each which would be fatal to adults.

These little patients, of course, require a larger carbohydrate, protein,

As stated above, if after three to five days on a "maintenance diet" the patient fails to show a marked change towards normal, insulin is indicated.

In a recent series of two hundred cases at the Diabetic Clinic at the Presbyterian Hospital 50 per cent required insulin. In a like number of private patients 46.2 per cent required insulin.

It need scarcely be stated that insulin is for all practical purposes inactive if given by mouth, by rectum, by inunction, by inhalation, by nasal tampon, by duodenal tube, or sublingually, or that there is no substitute which can be given by mouth for insulin.

The exact dose of insulin required in any given case is impossible to foretell and must be arrived at through careful attention to the laboratory findings. It is, of course, safer to adjust the insulin dose by blood sugar determination than by urinalysis.

A method which we have found satisfactory in determining the initial dose is to start with:

10 units a day if blood sugar is below 200
20 units a day if blood sugar is between 200-250

30 units a day if blood sugar is between

250-300

40 units a day if blood sugar is above 300

This scale, of course, must be adjusted according to developments and is no criterion of the final maintenance dose. If one were compelled to state the dose of insulin in any given case the answer would be "enough to control blood sugar."

If only up to 15 units are required, it can be given in one dose before breakfast. If more than 15 units and less than 40 units are required, it can be given in equal doses before breakfast and before dinner at night. If more than 40 units are required, it may be given before each meal, although it is safer to give larger doses before breakfast and supper and a smaller dose before lunch. Frequently it may be necessary to give a fourth dose at midnight and a fifth dose at 3 a.m.

The site of injection, of course, should be varied, and the smallest volume of insulin used, although the U-20 is probably the best strength to use routinely.

There are two types of reactions which are seen with the use of insulin. The first of these is the protein reaction. This may vary from a mild localized reaction to a rather severe generalized urticaria. Protein reactions are comparatively infrequent but they occur often enough for us to be on our guard against them. In many cases they can be avoided by changing the brand of insulin which is used.

The second and more common reaction is the hypoglycemic reaction or insulin shock, which results when the dose of insulin given is too large to be

balanced by the carbohydrate available at the moment in the body.

Insulin reactions usually develop from thirty minutes to three hours after the injection is given, although we sometimes note a delayed reaction occurring six to ten hours after the last administration.

The usual symptoms of insulin shock are inward tremors, hunger, nervousness, sweating, rapid pulse, subnormal temperature, diplopia, amnesia and coma. While these are the usual symptoms, it must be emphasized that any unusual emotional or nervous symptoms developing in a patient taking insulin should be regarded with suspicion. I will cite one instance of this:

This patient was a thin man of about 110 pounds in weight, whose blood pressure was seldom above 115 mm. of mercury, a man whose usual demeanor was mild and who was careful never to offend his friends or neighbors. One night, immediately after dinner, he got up from the table and staggered up the stairs complaining about the furnishings of the house, about his neighbors and bragging about his own importance. Upon reaching his bedroom he began to move the furniture about, displacing many pieces which ordinarily he could not have so much as budged. He became more and more abusive and finally his wife had to call in two of the neighbors to control him. A neighborhood physician was called, who gave him one-quarter grain of morphine, without diminishing his enthusiasm or strength. When I was called to see him he had struggled with these two husky young neighbors until they were practically ex-

hausted. We induced him to drink orange juice and gave him adrenalin by hypodermic. Shortly following this treatment he became rational again and expressed surprise at his former attitude.

Attacks of this type constitute a recognized form of insulin shock, and unless we are on our guard they may be mistaken for hysterical episodes and the treatment be misdirected.

Insulin shock is a condition not to be regarded lightly nor to be induced if it can be avoided. There have been recent reports of patients who have died of coronary attacks as a result of insulin shock. In elderly diabetics, par-

ticularly, every precaution should be taken to prevent the occurrence of all hypoglycemic reactions.

In conclusion, if there is any doubt as to whether a patient is in diabetic coma or is suffering from insulin shock the case should be considered as one of hypoglycemia and glucose should be administered by mouth or vein. If the case should prove to be one of diabetic coma little damage will have been done. If, however, it is one of hypoglycemia a life may have been saved.

REFERENCE

- ¹BEARDWOOD, J. T., JR., and KELLY, H. T.:
Simplified diabetic management, 1931,
J. B. Lippincott Co., Philadelphia, 67.

Insulin Hypoglycemia*†

Two Cases with Convulsions; One Necropsy Report

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THE reaction of the body to hypoglycemia, caused by unbuffered insulinism of endogenous or exogenous source, constitutes a recent chapter in medicine. This communication deals chiefly with this response as it occurs in the treatment of diabetes with insulin.

We have divided the insulin reaction into two phases, largely for the sake of convenience of description. The first is characterized by nervousness, perspiration, pallor, tremor, palpitation, weakness, hunger, and a peculiar sense of "goneness". The second indicates a disturbance of the central nervous system and presents a wide variety of symptoms. Of these the most frequently observed are diplopia, paresthesias particularly of the face and tongue, mental confusion, drowsiness, ataxia often simulating that of alcoholic intoxication, a vacuous, staring countenance, amnesia, and coma from which the patient cannot be aroused. Other manifestations less frequently encountered are dysarthria,

mixing of words, strabismus, hemianopia, loss of sphincter control, automatism, crying and singing, negativism, excitement or anger, giddiness, vomiting, garrulity, apraxia, aphasia, hemiparesis, temporary incorrigibility, behavior defects, tonic and clonic spasms of the extremities, opisthotonos and epileptiform convulsions. Many variations and combinations of these may occur in a reaction. The manifestations do not appear in any fixed type of sequence; nor does any one patient always exhibit the same type of reaction. The usual prodromal symptoms of the first phase may apparently be absent in some cases, or at least they are so brief in duration as to escape the attention of the patient. People accustomed to being about patients who are taking insulin can, however, often detect the characteristic countenance or behavior before the patient himself is aware of his state.

We present résumés of the following illustrative cases.

(1) A school teacher took her usual dose of insulin but did not eat her regular breakfast because she was not at home. While standing before her class she suddenly lost equilibrium, pitched forward, and was later admitted to hospital with a gash over one eye.

(2) A man, who had been taking insulin without trouble for three years, went to an

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†From The Buffalo General Hospital and School of Medicine, The University of Buffalo.

entertainment at his club. He took his regular dose of insulin, 18 units, just before departing from home. The dinner was delayed for over an hour and he did not care to ask for food. During the first course he felt giddy, collapsed and vomited several times. He was quite confused when admitted to hospital. There he behaved queerly, became very intimate and called one of us, with whom contact had always been formal, by his first name.

(3) A woman, who had been under treatment for nine years, usually knew when a reaction was coming on, yet could not bring herself to take the sugar which she always kept in her handbag. She was once taken to the police station on the charge of intoxication.

(4) A young man took his usual dose of insulin in the early morning and returned to bed. As it was Sunday the family slept late. He was found later in a convulsive state, but he promptly responded to glucose given intravenously.

(5) A man of thirty took his usual dose of insulin and his breakfast, shoveled considerable snow, and went to his business. At 1 p.m. he was found asleep by the police in his parked automobile. He was carried to a doctor's office in a state of coma and was given glucose intravenously. This immediately brought him out of the coma. He remembered nothing for at least an hour previous to this experience. Later he recalled that he was driving his automobile about four miles distant from the place where he was found, but he could recollect nothing which had occurred between that time and his recovery. He apparently drove this distance successfully while in an "automatic" state, resembling a fugue.

(6) A woman of sixty-two, who had been under insulin treatment for eight years, developed headache, difficulty of speech, and vomiting soon after breakfast. Six months prior to the present attack, she had had a right sided hemiplegia which had left but little residual damage. In the present attack coma followed closely after the symptoms which have been described, and when she was seen thirty minutes after the onset she was completely unconscious, with stertorous breathing and a sharp deviation of

the eyes to the left. The pupils were not dilated. Her blood pressure was lower than usual, 150 mm. of mercury systolic and 80 mm. diastolic. Unfortunately, a blood sugar determination could not be made. Ten grams of glucose in a 50 per cent solution were administered intravenously. Fifteen minutes later there was no change in her condition. However, within the next hour she gradually regained consciousness; occasionally she awoke momentarily and stared at those in the room. Two hours later she was normal again and able to take food. Then it was discovered that she had fever and a "grippe" infection, which had probably been the cause of the vomiting attack. Hypoglycemia was the probable cause of her symptoms. The family stated that she ate candy during the premonitory stage, but the patient had no recollection of anything from breakfast to lunch time.

In the insulin treatment of diabetes it is often necessary to give rather large doses in order to keep the patient's urine reasonably free from sugar. It is often a most difficult problem to achieve this in a patient in whom the diabetes is severe. Variations in the concentration of blood sugar are marked during the twenty-four hours, and the administration of insulin must be so planned as to counterbalance them. Since an attempt is always made to return even a severe diabetic patient to his normal position in society, it is often impossible for him to keep either on a perfectly standardized program or to keep the level of his physical exercise constant. Unusual muscular activity is one of the most common causes of insulin reactions. Hypoglycemia occurs very frequently on Sundays or holidays, when a patient's usual program is interfered with by the irregularity of meals and exercise.

Fatal Cases of Insulin Hypoglycemia

mia. Considering the above mentioned difficulties and the alarming symptoms which may be produced by insulin, it is rather interesting that so few reports of fatal cases have appeared in the literature.

JOSLIN¹ reports the following four cases that have come to his attention:

(1) A woman of 51 with gangrene and sepsis, who was seen in consultation, had received 240 units of insulin daily. She was unconscious and her blood sugar was 15 mgs. per 100 c.c. Glucose brought her out of coma twice, but she later succumbed. Insulin might have been but a secondary cause of death in her case.

(2) A woman, who apparently became alarmed at her symptoms, injected 122 units of insulin on her own responsibility during one night. She died in spite of glucose injected intravenously and subcutaneously.

(3) A man of 20, who had been living quite carelessly, took large doses of insulin to counteract his dietary indiscretions. He became comatose rather suddenly one evening and was given 60 units of insulin during the night. In the morning his blood sugar was too low to read. He died about fifteen hours after the inception of symptoms.

(4)² A girl of 14 ate less than her usual meal one evening. At 2 a.m. she was found in a convulsive state. During the succeeding fifteen hours, 300 units of insulin were administered. She died a day later in a state of tetanic convulsions.

HEIMANN-TROSJEN AND HIRSCH-KAUFFMANN³: A girl of eight, whose diabetes was severe and difficult to control, was admitted to hospital with convulsions. She was taking 50 units of insulin daily. Her blood sugar on admission was 20 mgs. per 100 c.c. The convulsions temporarily disappeared following the intravenous injection of two grams of glucose. Later on the same amount of glucose failed to relieve them. She was unconscious for twelve hours before death occurred. During this period convulsions occurred frequently. Glucose (107 grams) was given intravenously, intraperitoneally, and by gavage. The greater part of the glucose, however, was administered after the convulsions had been recurring for at

least six hours. The blood sugar, when taken an hour after a glucose injection and two hours before death, was 52 mgs. per 100 c.c. The necropsy, forty-eight hours post mortem, showed status thymico lymphaticus, enlarged Peyer's patches, colloid goiter, an adenoma of the cortex of the adrenals, and cysts of the ovaries. The central nervous system was not examined.

CAMPBELL AND MACLEOD⁴: (1) A habitual drunkard, who was refused insulin at the Toronto General Hospital, was treated elsewhere. He took his usual morning insulin, 30 units, but not feeling inclined to eat he proceeded with his day's activities. About midday he collapsed and was taken to hospital. Upon admission he was cyanosed, had edema of the lungs, and died before glucose could be administered. There was no necropsy, so the exact nature of his death was unknown, although hypoglycemia seemed a likely cause.

(2) A patient, whose insulin dosage was 40 units, had a gastrointestinal upset and took an additional 10 units of insulin. Shortly after, she recognized symptoms of hypoglycemia, took orange juice, and summoned her physician. He advised that more antidote be taken, but the suggestion was unheeded. The patient died in collapse shortly after.

PEMBERTON⁵: The patient had tuberculosis and diabetes. In the first attack of hypoglycemia there was muscular rigidity, opisthotonos and vomiting, which lasted five minutes. The second attack was ushered in by a period of physical and mental excitement, which was followed by muscular flaccidity and a semicomatose state. The eye balls showed pendulous movements. The corneal and abdominal reflexes were absent. There was a bilateral ankle clonus and Babinski response. The patient died a few moments later. Necropsy done the following day showed caseous pulmonary tuberculosis and fibrosis of the pancreas. The brain was described as being definitely wet.

MEMBREZ AND RAZDOLSKY⁶ (Non-diabetic patients who were given insulin and glucose):

(1) A very emaciated man of 50 years was admitted to the surgical service. He was given 40 grams of glucose intravenously and 0.5 c.c. of insulin (units not stated). The

following morning he received a blood transfusion of 500 c.c. and on that evening 40 grams of glucose intravenously and 1 c.c. of insulin. One and one-half hours later he felt chilly, became pale and later had fever. He was very weak, had a small pulse, perspired, and developed tonic spasms of the hands. Coma soon occurred. He was given injections of camphor, digitalis, and epinephrine, which brought no improvement. The next day his condition was considered grave. He was given 1,000 c.c. of salt solution intravenously and another blood transfusion of 500 c.c. Examination at this time showed his pupils to be dilated and his eyes staring. The knee jerks were active; a double Babinski response was present, the left being more active than the right. The right abdominal reflex was greater than the left. There was rigidity of the neck and of the muscles of the extremities. The spinal fluid, obtained by cisterna puncture, was clear and came out in drops. Sugar in the spinal fluid was 78 mgs. and the blood sugar 178 mgs. (It is not stated whether these tests were simultaneous, but they were done on the same day, four days after the insulin was injected.) The following day the patient was conscious and would raise his hands after commands. There was still some muscular rigidity and there was incontinence of the bladder. Since he did not improve, he was given 0.5 c.c. of insulin without glucose the following day. In two hours the patient was again comatose, but had no convulsions. He died in a short time of cardiac failure.

Necropsy Report. Acino-nodular and ulcero-fibrotic pulmonary tuberculosis; passive congestion of the liver, spleen, kidneys, meninges and spinal cord; hyperemia and edema of the meninges.

(2) A woman of 50 was admitted to the surgical service because of symptoms of intestinal obstruction. At operation a tumor of the intestine was found and an entero-anastomosis was done. She was in good condition on the fifth day following operation. Five hundred c.c. of a 10 per cent solution of glucose intravenously and 0.5 c.c. of insulin were given. That night she developed tonic contractions of the fingers, her jaws were set, eyes were turned to the right and upward, and the pupils did not react to light.

There was rigidity of the neck and other muscles. The tendon reflexes of the upper extremities were increased and those of the lower extremities diminished. The protective reflexes were absent. Coma followed. She was given 500 c.c. of glucose solution subcutaneously. Later on she became conscious, but remained very weak. The next day the pupils were equal, speech was slow and weak. A positive Oppenheim response was present on the left. The following day she received 600 c.c. of glucose solution subcutaneously and 0.5 c.c. of insulin. Her condition remained satisfactory for the next week, when nausea and vomiting appeared. She was then given 500 c.c. of 10 per cent solution of glucose intravenously and 0.5 c.c. of insulin. Three hours later she became very weak and had cramps in the hands; in six hours she was unconscious, perspired profusely and died the following morning of gradually increasing heart failure.

Necropsy Report. A well-built woman. Carcinoma and stricture of the intestine; metastases in the ovaries and omentum; edema of the brain.

WHITE AND SMITH⁷:* A boy of eight, who had been diabetic for four years, had been taking insulin for three years. In July 1930, he developed whooping cough. The insulin dosage had to be increased from 9 to 34 units daily. On August 17 a mild insulin reaction occurred, so the insulin was reduced to 28 units. On the evening of August 21 he was awakened by a paroxysm of cough. He cried out and complained that he was unable to see. The blood sugar was not taken, although an insulin reaction was suspected. He was immediately given, by mouth, 120 grams of orange juice and 10 grams of glucose, but restlessness and noisiness continued. One hour later he vomited. Throughout the night, glucose by mouth was given at frequent intervals and he received two injections of epinephrine 1-1,000 (0.3 c.c.). The symptoms did not change. He vomited again and by morning he was irrational. At 8 a.m. he was restless, his eyes were wide open and his face was ex-

*Drs. Priscilla White and Bertnard Smith kindly furnished us with the data of this case.

pressionless. He did not seem to comprehend. The rectal temperature was 105.0° F. He was then given 10 grams of glucose intravenously. The blood sugar at 10 a.m. was 250 mgs. He received 10 grams of glucose intravenously again, and at 11 a.m. the blood sugar was 580 mgs. Insulin, 12 units, was given upon the receipt of this report. Physical examination showed no abnormal neurological signs. The temperature remained high and the clinical state did not change. At 7 p.m. the spinal fluid showed some increase in pressure, but was clear and showed no increase of cells. At 9 p.m. he had mild convulsive twitchings. His blood sugar was 110 mgs. Ten grams of glucose were again given intravenously. The following day examination by a neurologist showed only an overfilling and pulsation of the retinal veins, an absence of the knee and ankle jerks, and a questionable right Babinski response. In the opinion of the examiner the condition resembled cerebral edema more closely than anything else. That evening he had a convulsion lasting one and one-half minutes; his body was rigid, the head was retracted, eyes were open, the hands were clenched and he foamed at the mouth. Another shorter convulsion came on during the night. The temperature continued high, 104.0°-105.0° F. At 11:30 the next morning he had a series of convulsions, one every 10-15 minutes. They started in the right arm; the mouth and eyes were drawn to the left. At 12:30 the convulsions were occurring every 2-5 minutes, but became less frequent before death, which occurred at 2:55 p.m.

Necropsy Report. "The brain shows marked thickening of the arachnoid and dilation of the arachnoidal vessels. There are scattered foci of degeneration with edema, scattered lymphocytes and oligodendroglia. In many places there is marked ependymal edema, and in rare foci dislodgement of the ependyma. In one of these foci there is a slight amount of pigmentation."

ALLAN AND WILDER⁸: A child of four received 95 units of insulin over a period of fifteen hours because of diabetic coma. The child retained consciousness, sat up in bed,

later became unconscious. Twenty units insulin were given but unconsciousness

continued. Six and one-half hours later hypoglycemia was suspected. Glucose intravenously, subcutaneously, and by rectum was administered immediately, but death occurred soon afterwards.

ROSENDAHL⁹: A severely emaciated diabetic patient with bilateral pulmonary tuberculosis. The first attack came on following two units of insulin, but subsequent attacks appeared after insulin was discontinued, in spite of increasing the diet. The patient was hypoglycemic at the time of death.

Necropsy Report. A completely sclerotic pancreas with calculi in the ducts. No island tissue was found. The liver showed a slight cirrhosis. The brain was not sectioned.

WOHLWILL¹⁰: (1) A woman of 62, who had been diabetic for at least two years, was admitted to hospital with an abscess of the breast, which had developed within three days. During this period she had received 100 units of insulin daily. Upon admission she was in deep coma, and also presented weakness of the left lower face. The diagnosis at first was a cerebral accident, but later this was changed to hyperinsulinism. She expired on the fourth day after admission.

Necropsy Report. The pancreas contained a considerable amount of fat. Cystopyelonephritis and mastitis were found. The brain was dry and brittle; otherwise, no pathological changes were discovered in the central nervous system. The facial weakness could not be accounted for.

(2) A woman of 29, who was known to have had diabetes for fifteen months, was admitted to hospital in typical diabetic coma. On the first day 135 units of insulin were given; on the second day, 70 units, and on each of the third and fourth days, 90 units. Consciousness returned on the fourth day, but she was completely disoriented. The breathing continued to be labored and the breath was described as uremic. Under treatment the blood sugar dropped from 462 mgs. to 65 mgs. and the glycosuria completely disappeared. The mode of death was not mentioned in the author's report.

Necropsy Report. Typical glycogenic degeneration of the kidneys. Extensive pulmonary emphysema. The brain was described as dry, but not as brittle as in the first case.

There was a generalized ganglion cell change which resembled the severe degenerative change of Nissl. There was a marked reaction of the glia, varying from a disappearance to a pyknotic change in the nuclei and the loss of the staining affinity of the processes of these cells. Many ameboid glia cells were scattered throughout the nervous tissue. In a few areas an unusual change in the axis cylinders was seen. This consisted in a swelling of the fiber and a dulling of its staining quality. The author questions whether this change might not have occurred after death.

COMMENT

We have included these two cases in this report because they were listed by Wohlwill as caused by insulin overdosage. The clinical data of both cases are incomplete, but the first obviously was complicated by a pyemic process and the second might have had concomitant uremia.

Early in the insulin era it was soon learned that emaciated diabetics, who were then so common, were sensitive to even small doses of insulin. Wood-yatt¹¹ mentions the development of hypoglycemic convulsions in such a patient who was receiving a diet and calculated doses of insulin. The blood sugar was too low to read. The patient died in coma in spite of restored glycemia and glycosuria. Williams¹² had a similar experience with one patient. He has kindly written us that he knows of two other patients in his vicinity who have succumbed to insulin hypoglycemia.

Gammon and Tenery¹³ have recently reviewed the subject of spontaneous hypoglycemia. Of the twenty cases classified as hyperinsulinism, due to adenoma or carcinoma of the islands of Langerhans, five have died. The following patients were necropsied:

THALHIMER AND MURPHY¹⁴: Carcinoma of the islands of Langerhans. The patient had frequently recurring convulsions followed by coma. Death occurred while the patient was in coma. *Necropsy Report*. The leptomeninges and the convexity of the brain showed slight or moderate swelling and moderate congestion of the vessels. Careful section of the brain showed no other abnormality.

MCCLENAHAN AND NORRIS¹⁵: The patient died in hypoglycemic coma in spite of large amounts of glucose which did not effectively raise the blood sugar. *Necropsy Report*. An adenoma of the islands of Langerhans. The brain showed perivascular round cell accumulations.

NADLER AND WOLFER¹⁶: Extensive primary carcinoma of the liver was found. Glucose was withheld at the final attack, at which time the blood sugar reached 13 mgs. per 100 c.c. Cheyne-Stokes respirations appeared and death occurred in coma two and one-half hours after the inception of the attack. This patient had had many attacks and his blood sugar had been very low, but convulsions had never occurred. *Necropsy Report*. (Dr. F. D. Gunn) The brain showed no macroscopic edema.

CASE REPORTS

Case I. F.W., a restaurant owner, aged 32. In February 1930, he was first admitted to hospital in diabetic coma. He had had diabetic symptoms for a month prior to this admission. He was discharged in two weeks on a diet of 1700 calories and 100 units of insulin daily. He was seen but once after his discharge, when he was given an increase of diet and advised to reduce his insulin gradually.

On June 1 we were summoned to his home in the country because he was again in coma. It was learned that he had been drinking heavily. The evening before he had complained of dizziness and nausea. Nevertheless, he had taken his evening dose of insulin and had gone to his room; it was not determined whether the evening meal had been taken. Later he was found in a semicomatose state, breathing slowly and perspiring heavily. He was given 30 units of insulin but no food. At midnight he was given 20 additional units, as his friend stated that he

was getting restless. Shortly afterwards he lapsed into unconsciousness. He had a convulsion during the early morning hours. When one of us (B.D.B.) saw him at 9 a.m. he was very restless, excited, and incorrigible. It was necessary for his attendants to restrain him. It was estimated that he had received from 70 to 100 units of insulin since the night before and that no food had been given. He was given 20 grams of glucose intravenously without change in his clinical condition. A half hour later his blood sugar was taken, which proved to contain 98 mgs. per 100 c.c. Then 30 additional grams of glucose were given intravenously. At twelve o'clock the ambulance doctor gave him 20 additional grams. As soon as he was admitted to hospital he received 20 more, at which time he showed some signs of waking up when stimulated. Further attempts to give glucose intravenously were unsuccessful, because he was unmanageable. The following note was made in the afternoon. "The patient is very much confused, but not delirious. His remarks are stereotyped, often short phrases which are repeated frequently. He lapses into sleep after being aroused. The neurological examination is negative." At 9 p.m. he was again given 20 grams of glucose intravenously. He then was beginning to take some fluid by mouth. His blood sugar, one-half hour later, was 308 mgs. per 100 c.c. His bladder was extremely distended and it was necessary to catheterize him. It required three men to hold him down during this procedure. He was then given 10 units of insulin every three hours, followed by 200 c.c. of orange juice by mouth. The following morning his mentality seemed clearer and his comprehension better. His blood sugar was 222 mgs. per 100 c.c. It was necessary to continue the glucose intravenously because it was impossible to get him to take the orange juice. By evening he recognized some of his friends. On the morning of June 3 he was mentally clear, but slow. He was able to take food. It was then learned from friends that in August 1929, before the onset of diabetic symptoms, he had an attack of repeated epileptiform convulsions, which came on while driving an automobile and while on his boat. He had been drinking

heavily before the present attack. He was discharged on June 6, at which time his mental condition, as far as memory, insight, and judgment were concerned, was good. His neurological examination remained negative.

Comment. Alcoholic intoxication did not seem to account for his reaction. It seems probable, on the other hand, that because of the large amount of insulin which he had had and the extreme rarity of true epilepsy in the diabetic, his symptoms were related largely to hypoglycemia.

Case II. E.D., a boy of 16, who had been under our observation since a few weeks following the inception of diabetes three years before, was brought to hospital March 21, 1931, in "status epilepticus". He had been a faithful patient and had visited the out-patient clinic two weeks previously, when it was found that his blood sugar was 54 mgs. per 100 c.c. at noon. His insulin dosage was then decreased from 32 units daily to 28; his diet was unaltered—135 grams of carbohydrate, 60 grams of protein, and 140 grams of fat. He had had no insulin reactions recently. Both of the patient's parents were deaf and dumb, but he was normal in all respects and got along very well at school. It was learned that on March 20 he roller-skated from 8 to 10 p.m., during which time he fell on his left shoulder and side of his face, producing only a minor skin abrasion on his forehead. Upon arrival home his arms and jaws twitched. The parents thought that diabetic coma was impending and gave him 36 units of insulin. He continued to twitch in his sleep all night, vomited a few times, and refused food. Because he was not improved by morning 18 units of insulin were given at 8 a.m. and repeated at 10 a.m. He had about six convulsions during the day and, according to the father's statement, was a "little unconscious". During a period of two hours after admission he had a series of about fifty major convulsions with the following sequence: cessation of breathing, cyanosis, turning of eyes to the left with nystagmus, wrinkling of forehead, twitching of the right side of face, tongue moving in and out, rigidity of

arms with hands forcibly adducted at the wrists, rigidity and extension of the legs, flaccidity and occasional clonic spasms of the entire body. In the short interim between attacks he remained totally unconscious. His blood sugar on admission was 43 mgs. He was given 170 c.c. of a 50 per cent solution of glucose intravenously during the first four hours after admission, but the convulsions did not cease until sodium luminal 0.12 grain was given intravenously. His blood sugar an hour after the last injection of glucose was 46 mgs. per 100 c.c. Glucose intravenously was continued at intervals all through the night. Total night amount, 110 c.c. of 50 per cent solution. There was occasional emesis, but consciousness was not regained. Spinal fluids, obtained on the evening of admission and the next morning, were tinged with blood; they were not under pressure. The glucose content of the first fluid was 80 mgs. and of the second, 111 mgs. per 100 c.c. The chloride content of the second was 816 mgs. per 100 c.c. The record of the temperature, pulse, respiration, and blood pressure are shown on the accompanying chart. The day after admission the red cells were 4,300,000 per cu. mm., hemoglobin, 70 per cent, leukocytes, 12,000, with 81 per cent of polymorphonuclears. On March 22 he had two convulsions fifteen minutes apart. Sequence: dilatation of the pupils, turning of the eyes to the left, severe twitching of the right face, twitching of the left thumb and the left arm, elevation of the left arm to a right-angled position and, finally, a sharp contraction of both pupils to pin point size. During the following three days he showed no signs of regaining consciousness. His temperature, pulse rate, and respiration rate rose. On March 23 signs suggesting meningeal "irritation" developed—questionably positive Kernig and Brudzinski signs, but no rigidity of the neck. There was an absence of the deep reflexes as well as of the plantar responses. On March 24 two cisterna and two lumbar punctures were done; very little spinal fluid could be obtained and that was again slightly bloody (traumatic?). Insulin, glucose and physiological saline solution subcutaneously were kept up during March 22, 23, and 24. He died on March 25.

Necropsy. (Dr. Kornel Terplan)*

General. The body is that of a slender, well-developed boy of 16 with very little adipose tissue. There are small excoriations of the skin on the right temple and the right occipital region. Upon examination underneath these abrasions no hemorrhage or alteration of tissue is found. There is no fracture of the skull or injury to the dura mater.

Brain. The pachymeninges above the cerebrum are markedly distended. The brain is pressed closely to them and shows a very extensive degree of swelling. The veins in the leptomeninges are distinctly injected. The sulci are entirely obscured and the gyri greatly enlarged and flattened. The brain is heavy—weight, 1535 grams. On cross section there is a very marked hyperemia and extensive edema in all parts of the cerebrum and cerebellum. The tonsils of the latter are, also, distinctly swollen. The cerebellar leptomeninges, in the posterior part of the tuber vermis, show a small intrameningeal suffusion. The ventricles are distinctly diminished in size, being compressed by the swollen brain substance. They contain almost no spinal fluid.

Spinal Cord. There are free hemorrhages on the posterior aspect of the pachymeninges in the fat tissue, but no free hematomata. The pachymeninges and cord are both distended and closely attached. There are small subdural hemorrhages along the spinal cord (cisterna puncture). The leptomeninges show no distinct sign of fresh hemorrhage. Sections of the spinal cord reveal a very marked edema. The leptomeninges are distinctly injected.

Spinal Fluid. (Cisterna puncture). Very small amount, blood tinged. Chloride content, 845 mgs. per 100 c.c.

Heart and Aorta. Normal size. There is a very slight fatty change in the intima of the ascending aorta and in the branches of the left coronary artery.

Pancreas. Rather narrow and small. Weight, 34 grams. Shows distinct hyperemia.

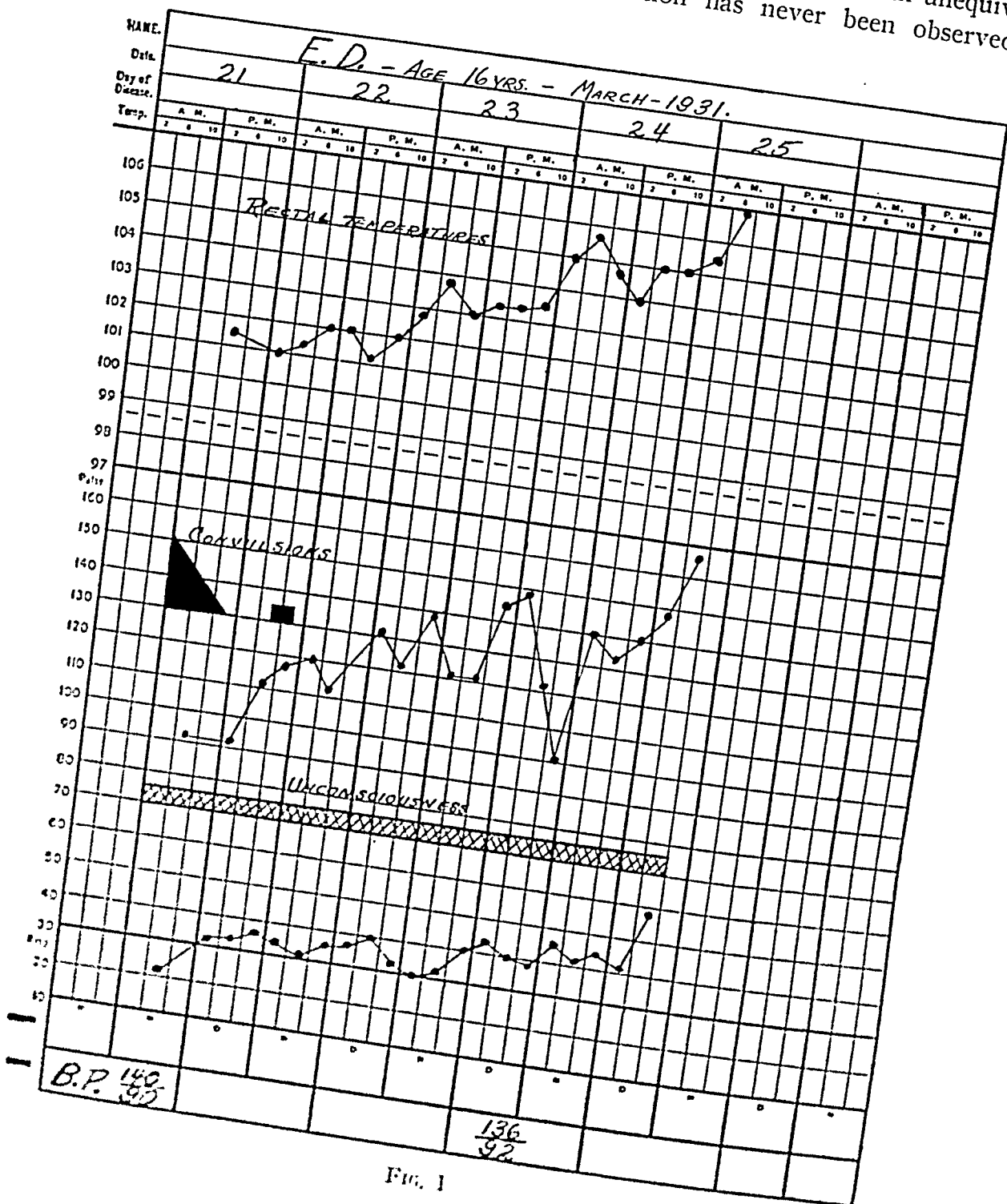
Suprarenals. Very large, showing considerable amount of lipoid in the cortex.

*To be reported elsewhere in more detail, together with the histologic findings.

THE NATURE OF THE HYPOGLYCEMIC REACTION

A low blood sugar is the usual accompaniment of the insulin reaction both clinically and experimentally, although good clinical observers have reported similar reactions in patients receiving insulin which have occurred

at a time when the blood sugar was well above the hypoglycemic level. John¹⁷ found hypoglycemia in only 54 per cent of his patients during reactions. The remainder had either normal blood sugar levels or hyperglycemia. In our experience an unequivocal reaction has never been observed in



the absence of hypoglycemia. On the other hand, we have frequently observed blood sugar readings below 60 mgs. without symptoms; one obese youth had a blood sugar of 26 mgs., yet had no complaints. Macleod¹⁸ observed an asymptomatic hypoglycemia in animals that had previously been well fed.

The similarity between the early symptoms of the insulin reaction and the epinephrine reaction was commented upon by several workers, but it was not until Cannon¹⁹ and his co-workers brought forth physiological evidence of an epinephrine discharge during hypoglycemia that this relationship was clearly established. Cannon showed that cardiac acceleration of the denervated hearts of animals occurred coincidentally with insulin hypoglycemia and that the cardiac rate fell promptly after the administration of glucose. This acceleration did not occur in the denervated hearts of the suprarenalectomized animals. Other evidences of epinephrine discharge during hypoglycemia are contained in the work of Abe, Houssay et al, and of Kahn.²⁰ The following symptoms, pallor, sweating, tachycardia and dilatation of the pupils, are evidence of a discharge of sympathetic impulses which is produced by epinephrine action. Cannon¹⁹ believes that this discharge is a protective mechanism which attempts to compensate for hypoglycemia by mobilizing glycogen from the liver.

The second phase of the reaction is of greater moment. The symptoms point to a disturbance of the central nervous system and often are of a nature indicating a focal disorder. The

nature of this mechanism is not understood. The Toronto physiologists early observed that the venous blood of hypoglycemic animals seemed darker than normal, which suggested that anoxemia might be the cause of the symptoms since convulsions are known to occur in asphyxia. Olmsted and Taylor²¹ investigated this phase of the problem, but found only a slight fall of the oxygen saturation of the arterial blood in dogs preceding insulin convulsions. They, moreover, were not able to duplicate these results in rabbits.

In our fatal case an extreme edema of the brain and spinal cord was found. Four of the six reported necropsies on patients who had died of hypoglycemia showed some degree of cerebral edema, though, judging from the reports, this was much less extensive than the edema found in our patient. Schereschewsky, Mogilnitzky and Gorjaewa²² seem to be the only ones who have made anatomical observations of the central nervous system in animals with induced hypoglycemia. They report hyperemia, edema, and hemorrhages of the brain in dogs that had received huge doses of insulin.

These findings suggest that hypoglycemia may be accompanied by a disturbance of the water or of the electrolyte balance. In this connection other observations offer some support to such a relationship. Olmsted and Taylor²¹ found that the oxygen capacity of the blood in decapitated and decerebrated cats indicated that the blood was most concentrated at the time when the blood sugar reached its lowest level. Rathery and Sigwald²³ studied the effect of insulin hypogly-

cemia in twelve dogs. They report a constant elevation of the plasma chlorides and a decrease in the spinal fluid pressure. Drabkin and Shilkret²⁴ found that convulsions did not occur in dogs that were made hypoglycemic by the injection of large doses of insulin if they had previously been dehydrated by water deprivation for several days. They, also, report that insulin increased the existing anhydremia. Drabkin and Ravdin²⁵ observed that the cerebrospinal fluid pressure of hydrated dogs that had received large doses of insulin, rose as the blood sugar fell and as the blood became concentrated. The intravenous administration of a hypertonic solution of sodium arabinatę to hydrated dogs, during a period when severe insulin convulsions were present, resulted in a temporary return of the concentration of the blood toward normal. The convulsions disappeared temporarily (30-45 minutes) even though severe hypoglycemia remained. They suggest that the mechanism in the production of convulsions proceeds in the following cycle: hypoglycemia→anhydremia→rise in cerebrospinal fluid pressure→convulsions. They removed both stellate ganglia from three hydrated dogs. In these, insulin failed to produce convulsions and hypoglycemia was appreciably delayed and its magnitude reduced. Also, neither anhydremia nor rise in the spinal fluid pressure occurred in these dogs. McQuarrie and Peeler²⁶ observed that convulsions may be induced in epileptic children by hydration produced by the ingestion of water and the injection of pitressin. This offers further evidence that cerebral hydration is a factor in the cause of

convulsions. Weir, Larson and Rowntree²⁷ injected pituitrin in antidiuretic doses and simultaneously gave large amounts of water, 50 c.c. per kilogram per hour, by stomach tube to dogs. The symptoms which followed—asthenia, restlessness, diarrhea, nausea and vomiting, tremor, salivation, twitchings of the muscles, ataxia, tonic and clonic convulsions, and stupor or coma—are largely referable to disturbance of the central nervous system. This disturbance is possibly hydration.

Olmsted and Logan²⁸ found that typical insulin convulsions could be induced in decerebrated cats, but not in decapitated cats, even though in the latter the blood sugar was maintained at a hypoglycemic level. In hypophysectomized-decerebrated cats the blood sugar fell rather rapidly after insulin, and convulsions ensued promptly; while in decerebrated cats, whose hypophysis was left intact, the blood sugar was found to be more resistant to the action of insulin. Cannon²⁹ has suggested that this effect is caused by an injury to the hypothalamic region which is produced by the operation of low-decerebration. Houssay and Bissotti,³⁰ however, have also called attention to the extreme sensitivity of hypophyseoprival dogs to insulin. Such animals, receiving doses of insulin that had no effect on control animals, died from hypoglycemia. Spontaneous hypoglycemia crises also occurred in these dogs. Olmsted and Taylor³¹ showed that typical hypoglycemic convulsions could be produced in decapitated cats by actively induced respirations and that these animals would have violent convulsions following the slightest stim-

ulus. This irritability disappeared after the injection of glucose. It would seem, then, that the factor responsible for the convulsions which are associated with hypoglycemia may act on the spinal cord as well as the mid-brain.

The more pronounced symptoms of the insulin reaction, which we have spoken of as the second phase, indicate a disturbance of the central nervous system. This disturbance is associated with a hypoglycemia and it seems evident that it is caused either by the hypoglycemia or by secondary changes, possibly physico-chemical in nature, which accompany it. The use of glucose intravenously in patients showing this phase of the reaction acts specifically and promptly if the symptoms have been of short duration. The fatal case that we are reporting and a number of those contained in the literature, demonstrate that the reaction within the nervous system may go to a point which is not reversible by the intravenous administration of glucose.

Lennox³¹ determined the fasting respiratory quotients of the brain, arm and leg by means of analyses of the O_2 and CO_2 contents of the regional arterial and venous blood. The average quotient for the brain was 0.95, for the arm, 0.86, and for the leg, 0.72. He also found that the difference in the venous and arterial blood sugar paralleled the respiratory quotients. These studies, in his opinion, suggest that the disappearance of glucose from the blood is greater in its passage through the brain than through the extremities. Myerson and Halloran³² made a similar study on psychotic patients with identical results. It would

appear from these observations that the brain required glucose in its metabolism to a greater extent than other tissues.

The retardation of an appreciable rise of the blood sugar after the intravenous administration of glucose in patients who had previously received large doses of insulin, strongly suggests that there is a mechanism of insulin storage in the body. Our two cases as well as others reported in the literature would seem to demonstrate such a protective phenomenon.

SUMMARY

We have been able to collect twenty fatal cases of hypoglycemia produced by the artificial injection of insulin. This number includes our own case and nineteen which we have found in the literature.

The cases of two diabetic patients with insulin hypoglycemia, which had been produced by the erroneous administration of large doses of insulin, have been reported. Both manifested symptoms referable to the central nervous system. The fatal case showed an extreme edema of the brain and spinal cord and a very small amount of spinal fluid at necropsy.

Suggestive evidence that the cerebral symptoms of the hypoglycemic reaction are caused by or related to a hydration of the central nervous system has been collated.

The mechanism of the relationship of this possible hydration to hypoglycemia is not understood.

Changes in the central nervous system, which are related primarily to hypoglycemia, may be irreversible if the restoration of normal or hyperglycemia is delayed. Patients manifesting

cerebral symptoms of an insulin reaction, in our opinion, are better treated by the prompt use of glucose intravenously rather than by the less dependable method of the use of carbohydrate orally.

The behavior of the blood sugar after the intravenous administration of glucose to patients who have received large doses of insulin, suggests that there is a mechanism of insulin storage in the body.

BIBLIOGRAPHY

- ¹JOSLIN, E. P.: Treatment of diabetes mellitus, 1928, Lea and Febiger, Philadelphia, 52-53.
- ²JOSLIN, E. P.: Control and treatment of diabetes mellitus, N. Y. State Med. Jr., 1930, xxx, 1461-1464.
- ³HEIMANN-TROSIEN, A., and HIRSCH-KAUFFMANN, H.: Hypoglykämie mit tödlichem Ausgang, Klin. Wchnschr., 1926, v, 1655-1657.
- ⁴CAMPBELL, W. R., and MACLEOD, J. J. R.: Insulin, Medicine, 1924, iii, 195-308.
- ⁵PEMBERTON, H. S.: Hypoglycemia, Brit. Med. Jr., 1925, i, 1004-1005.
- ⁶MEMBREZ, G., and RAZDOLSKY, I.: Über die Gefahren der intravenösen und subkutanen insulinführung. Zwei Fälle mit tödlichem Ausgang, Zentralbl. f. Chir., 1931, lviii, 1627-1631.
- ⁷WHITE, P., and SMITH, B.: Personal communication.
- ⁸ALLAN, F. N., and WILDER, R. M.: Causes of failure in the treatment of diabetes of children, Jr. Am. Med. Assoc., 1930, xciv, 147-152.
- ⁹ROSENDAHL, G.: Diabetes mellitus and hypoglycemia, Acta med. Scandinav., 1927, lxxvi, 100-108.
- ¹⁰WOHLWILL, F.: Über Hirnbefunde bei Insulin-Überdosierung, Klin. Wchnschr., 1928, vii, 344-346.
- ¹¹WOODYATT, R. T.: The clinical use of insulin, Jr. Metab. Res., 1922, ii, 793-801.
- ¹²WILLIAMS, J. R.: Personal communication.
- ¹³GARDNER, G. D., and TENERY, W. C.: Hypoglycemia: the clinical syndrome, etiology and treatment; report of a case due to hyperinsulinism, Arch. Int. Med., 1931, xlvii, 829-854.
- ¹⁴TRUMBULL, W., and MURPHY, F. D.: Carcinoma of the islands of the pancreas: hyperinsulinism and hypoglycemia, Jr. Am. Med. Assoc., 1928, xci, 89-91.
- ¹⁵MCCLENAHAN, W. U., and NORRIS, G. W.: Adenoma of the islands of Langerhans with associated hypoglycemia, Am. Jr. Med. Sci., 1929, clxxvii, 93-97.
- ¹⁶NADLER, W. H., and WOLFER, J. A.: Hepatogenic hypoglycemia associated with primary liver cell carcinoma, Arch. Int. Med., 1929, xlv, 700-710.
- ¹⁷JOHN, H. J.: The lack of uniformity in the insulin reaction, Am. Jr. Med. Sci., 1926, clxxii, 96-106.
- ¹⁸MACLEOD, J. J. R.: Carbohydrate metabolism and insulin, 1926, Longmans, Green and Co., Ltd., New York and London, 277.
- ¹⁹CANNON, W. B., McIVER, M. A., and BLISS, S. W.: Studies on conditions of activity in endocrine glands. XIII. A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia, Am. Jr. Physiol., 1924, lxxix, 46-66.
- ²⁰KAHN, in CORI, C. F.: Mammalian carbohydrate metabolism, Physiol. Rev., 1931, xi, 143-275.
- ²¹OLMSTED, J. M. D., and TAYLOR, A. C.: The effect of insulin on the blood. I. Changes in oxygen saturation, percentage hemoglobin and oxygen capacity, Am. Jr. Physiol., 1924, lxxix, 142-154.
- ²²SCHERESCHEWSKY, N. A., MOGILNITZKY, B. N., and GORJAEWA, A. W.: Zur Pathologie und pathologischen Anatomie der Insulinvergiftung, Endokrinologie, 1929, v, 204-224.
- ²³RATHERY, F., and SIGWALD, J.: Etude expérimentale des modifications humorales dans l'hypoglycémie insulinique chez le chien, Compt. rend. Soc. de biol., 1931, cvii, 1074-1076.
- ²⁴DRABKIN, D. L., and SHILKRET, H.: In-

- sulin anhydremia; importance of water-reserve in physiological crisis, *Am. Jr. Physiol.*, 1927, lxxxiii, 141-146.
- ²⁵DRABKIN, D. L., and RAVDIN, I. S.: Mechanism of convulsions in insulin hypoglycemia, *Jr. Biol. Chem.*, (Proc. Am. Soc. Biol. Chem.), 1930, lxxxvii, 3-4.
- ²⁶MCQUARRIE, I., and PEELER, D. B.: Effects of sustained pituitary antidiuresis and forced water drinking in epileptic children; diagnostic and etiologic study, *Jr. Clin. Invest.*, 1931, x, 915-940.
- ²⁷WEIR, J. F., LARSON, E. E., and ROWN-TREE, L. G.: Studies in diabetes insipidus, water balance, and water intoxication, *Arch. Int. Med.*, 1922, xxix, 306-330.
- ²⁸OLMSTED, J. M. D., and LOGAN, H. D.: The effect of insulin on the central nervous system and its relation to the pituitary body, *Am. Jr. Physiol.*, 1923, lxxvi, 437-444.
- ²⁹CANNON, W. B., quoted from MACLEOD, J. J. R.: Carbohydrate metabolism and insulin, 1926, Longmans, N. Y., p. 284.
- ³⁰HOUSSAY, B., and BIASOTTI, A.: Carbohydrate metabolism and insufficiency of hypophysis, (Buenos Aires letter), *Jr. Am. Med. Assoc.*, 1931, xcvi, 129-130.
- ³¹LENNOX, W. G.: Cerebral circulation; respiratory quotient of brain and of extremities in man, *Arch. Neur. and Psychiat.*, 1931, xxvi, 719-724.
- ³²MYERSON and HALLORAN: Cited by Lennox.

The Incidence of Tuberculosis in Diabetes*†

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THE patient with diabetes who attempts to give himself the best care is surrounded by restrictions and must always exercise considerable self-denial. He must be scrupulous in the care of his feet and regard seriously any skin infection no matter how trivial it may seem. He must exercise the greatest care to avoid contracting the ordinary acute infections, such as the common cold, grippe, and gastroenteritis. If he is intelligent his happiness is clouded by the fear of premature arteriosclerosis with all of its sad complications, such as retinitis, coronary disease, gangrene, etc. In the list of dangers which may threaten the diabetic must be included pulmonary tuberculosis inasmuch as some writers find evidence that the diabetic may be unduly susceptible to this disease.

Joslin,¹ in his textbook, states that in his experience tuberculosis in diabetics seldom occurs in private practice today. Charles Montgomery² believes that there is no conclusive proof that tuberculosis is more common in diabetics than in the rest of the population of like age period. Boswell³ states that he too finds no greater incidence of tuberculosis among diabetics than among non-diabetics of like age period.

J. H. Musser, Jr.⁴ states: "This combination of disease is rather unusual as tuberculosis is not more frequent in the diabetic than in the normal individual".

There are others, however, who do not hold to this comforting opinion. Griesinger⁵ more than 70 years ago reported 250 cases of diabetes with 42 per cent showing tuberculosis. Windle⁶ found 50 per cent of 327 cases to have died of tuberculosis. Fitz⁷ quotes Copeland and Bardsley in the early nineteenth century to the effect "that tuberculosis occurred so frequently in diabetics as to be a sign of this disease". These statistics and opinions, of course, are influenced by the much greater frequency of tuberculosis in the general population at that time and also by the poor treatment which was given to diabetics at that time. Fitz and Murphy⁸ in 37 cases of diabetes examined postmortem found pulmonary tuberculosis to have been the cause of death in 19 per cent. Perhaps the most discouraging experience has been that reported by Sosman and Steidl⁹ in 1927. These workers made 261 separate roentgen-ray examinations of the chest in 182 consecutive cases of diabetes. These examinations revealed tuberculosis in 9 per cent of the cases. This was not, however, the usual apical type of tuberculosis but was of

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†From Diabetic Clinic, Medical Dept., Rhode Island Hospital.

such a characteristic appearance that at the Peter Bent Brigham Hospital it is spoken of as "diabetic tuberculosis". "It is bronchopneumonic in type, usually around the hila and deep in the lungs, strongly suggesting the type of tuberculosis seen in children or non-sensitized persons." It was usually accompanied by little or no physical signs. Sosman and Steidl regard this type of tuberculosis as a new infection and not the reactivation of an old infection. They found the prognosis uniformly bad.

More recently from the Mayo Clinic Adams¹⁰ reported the following: "Among the first thousand cases of diabetes studied after 1922, there were ten cases with signs of active pulmonary tuberculosis. Of these ten, seven are now dead in spite of the most careful treatment of the two diseases. Fourteen more of these first thousand developed active pulmonary tuberculosis after their first visit to the clinic." They concluded from these data that active pulmonary tuberculosis is a less common but more serious complication of diabetes than acidosis or gangrene. They find that tuberculosis is not as common as has been supposed.

"In the Peter Bent Brigham Hospital⁷ and its out-door department, from October 1, 1922 to January 1, 1929 there appeared 1,529 patients with diabetes." Of these, 35 had developed subsequent tuberculosis. "Joslin reports 43 cases of tuberculosis among his last published 3,000 cases." The combined number of these cases—Mayo Clinic, Brigham Hospital, and Joslin's—totals 5,500. This gives an incidence of 1.8 per cent of the total. Of the Brigham cases reported from

October 1922 to January 1929, 86 per cent are dead. Fitz tabulated as follows the duration of life in diabetics after tuberculosis is recognized (30 fatal cases):

- (1) One year or less—19 cases—63 per cent;
- (2) More than one year and less than three years—7 cases—23 per cent;
- (3) More than three years—4 cases—14 per cent.

We, in the diabetic clinic of the Rhode Island Hospital, have been interested in determining how frequently our patients are afflicted by tuberculosis, and our interest was increased especially by the report of Sosman and Steidl regarding the high incidence of a highly fatal type of tuberculosis. This clinic comprises 500 active diabetic cases who are seen at varying intervals. In general these people are of a poorer class such as one would expect to see in a free clinic, and as a group are probably comparable to the type of patients seen at the Brigham Hospital. They include people of various nationalities and of varying degrees of intelligence and coöperation. The disease in these patients is naturally of every degree of severity. We have available the roentgen-ray findings in 408 patients. We think it is noteworthy that in not a single case have we found the hilum type of tuberculosis described by Sosman and Steidl. We have found five active cases of tuberculosis in this group and are watching closely one patient whom we consider a potential case. In addition, two patients have been treated in the clinic who have inactive tuberculosis of the ordinary apical type. In both

of these patients the tuberculosis was present before the development of diabetes. Both of these patients are alive and well, one of them in spite of a severe diabetes which is well controlled. The patient whom we regard as a potential case of tuberculosis is a young

man also negative. Roentgen-ray examination of this patient made in 1928 was reported as follows: "Roentgen-ray of the chest shows no definite pathology". A second roentgen-ray examination made six months later was reported as follows: "The right

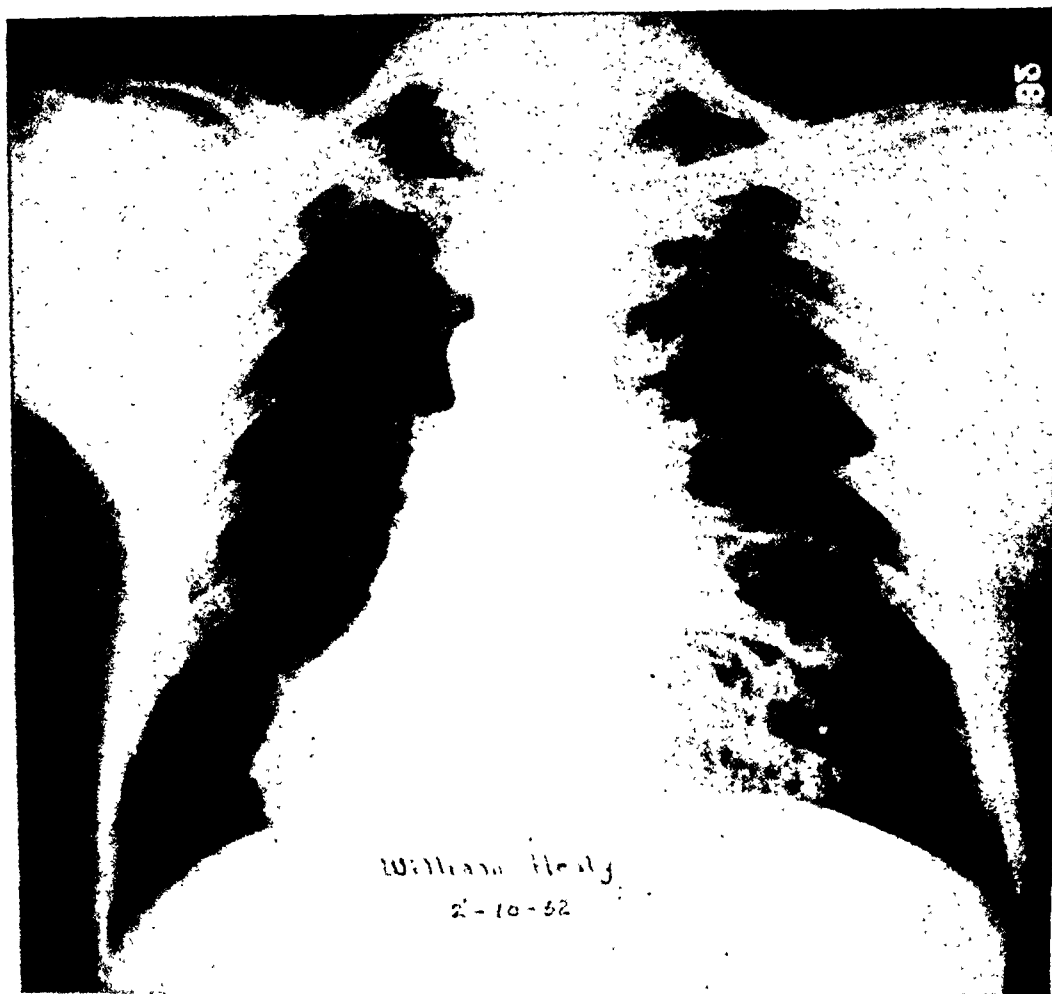


FIG. 1. Case W. H., February 1932.

man of 26 years of age, with severe diabetes who has reported undoubted hemoptysis. This patient also has a history of pleuritis sicca on several occasions in the past and also of gross hemoptysis four or five years ago. In spite of this history he has none of the ordinary symptoms of tuberculosis and physical examination is negative. A single examination of the sputum

costophrenic sinus is shallow. There is definite density of the structures in the region of the lung roots. There is abnormal density of lung markings in the midportion of the right lung. There are many small ring-like shadows in the lower lobe of the right lung suggesting dilated bronchi." Roentgen-ray examination made in February 1932 was reported as fol-

lows: "Examination of the chest shows generalized increased markings throughout the lung fields. There appears to be some beading of the markings upward into the apex. There is

CASE I

E. R., female, age 31, duration of diabetes nine years, of tuberculosis three years and ten months. X-ray findings in June 1928 were as follows: "There is an area of mottled dullness projecting outward from the



FIG. 2. Case II, July 1929.

a small area of dullness in the fourth interspace anteriorly. There are numerous small dense calcified areas in the region of the lung roots, particularly in the left, suggestive of previous healed infection." The roentgen-ray of the chest of this patient is shown in figure 1.

A brief résumé of our five active cases is as follows:

region of the great vessels into the right axilla and at the level of the second and third right anterior ribs. There is a large ring-like shadow in the second interspace probably due to a large cavity. Findings in this area suggest a lung abscess but could be due to a tuberculous process. There is dullness also in the lower lobe of the left lung just above the diaphragm shadow. No evidence of fluid in the left chest. The dullness in the left lower lobe could be due to tuberculosis. The dullness could be due to

consolidation also". This patient was treated very successfully by pneumothorax. She was discharged from the sanatorium within a few months and is doing very well. She is afebrile, has no cough or sputum and the disease is apparently arrested.

revealed scattered tuberculosis in the greater part of both lungs and a cavity in the left lung. The patient is afebrile, but has a persistently positive sputum. His general condition seems to be very good. "However, his prognosis can only be considered fair



FIG. 3. Case III, February 1930.

CASE II

J. H., male, age 64, duration of diabetes four years, of tuberculosis three years. Roentgen-ray findings July 17, 1929 (figure 2) were as follows: "There is a marked cloudiness and infiltration at the left top and right mid-chest and also definite mottling in the left base consistent with tuberculosis." The patient is in a sanatorium. The findings two years later, June 1931,

because of the danger of a generalized dissemination of the disease from the open cavity. He is sugar free or occasionally has a very slight trace of sugar in the urine on an ordinary diabetic diet without insulin."

CASE III

J. H., male negro, age 37, duration of diabetes seven years, of tuberculosis ten months. Roentgen-ray on February 18,

1930 and January 2, 1931 showed negative lung fields (figure 3). The patient, however, continued to feel badly, losing weight, etc., and another roentgen-ray taken July 1, 1931 showed the following (figure 4): "Examination of the chest shows extensive mottled dullness on the right between the

and is doing fairly well for a bilateral case. The outlook is still uncertain."

CASE IV

V. C., male, age 54, duration of diabetes six years, positive evidence of tuberculosis June 1932 when he began to complain of

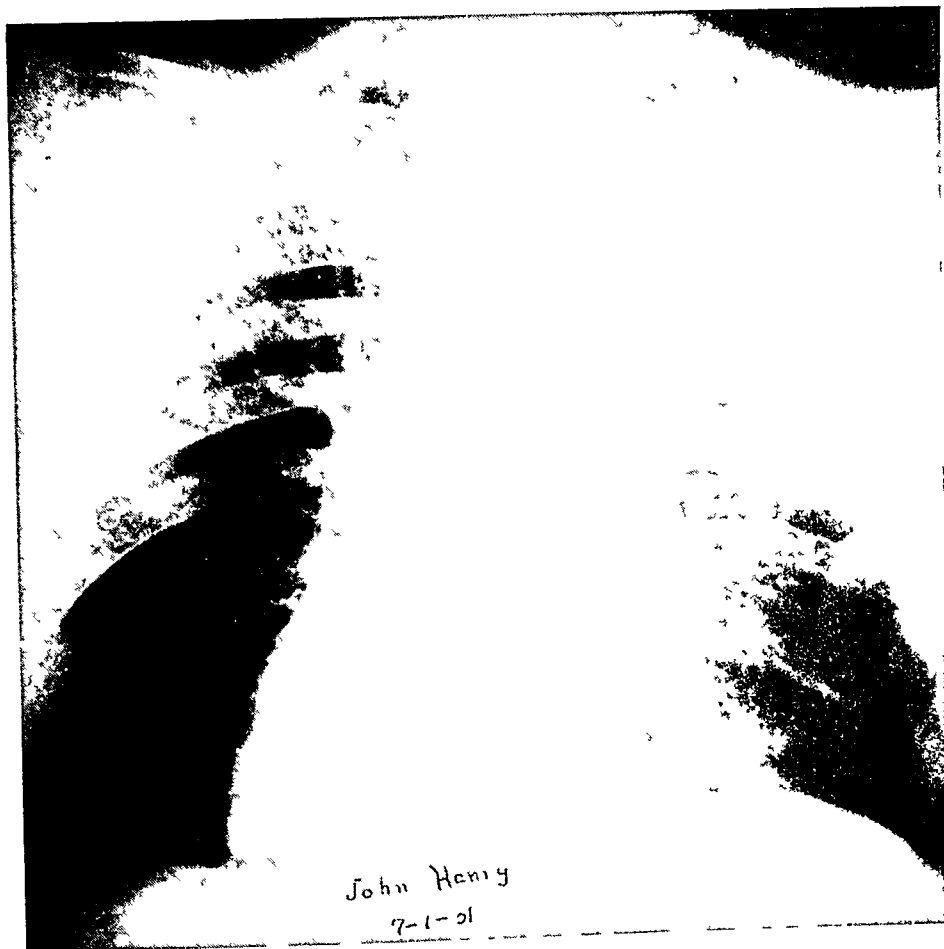


FIG. 4. Case III, July 1931.

third and fourth ribs anteriorly. The findings are those usually seen with a tuberculous process. The entire left lung is clear." He, too, is at present in a sanatorium. The latest report from the sanatorium is as follows: "In regard to the case of J. H., would say that he is taking 70 units of insulin daily, and usually has only a trace of sugar in his urine. He is a bilateral case and has not been given pneumothorax. He has gained ten pounds since admission

cough, loss of weight, and fatigue. His diabetes is of a mild nature. He is on a house diet excluding sweets, without insulin. He is at present in the Charles V. Chapin Hospital in the tuberculosis ward and is doing very well. He is afebrile and has shown only one positive sputum. Earlier in the course of his diabetes the chest roentgen-ray findings were negative, but a second roentgen-ray in June 1932 showed a tuberculous infection in the right upper lobe.

CASE V

B. C., age 50, duration of diabetes two years, of tuberculosis about fourteen months. Patient has family history of tuberculosis. Routine roentgen-ray examination in May 1931 was reported as follows: "Examination of the chest shows definite, fine increased density scattered throughout both

creased density of the bronchial markings, but no definite evidence of tuberculosis." She continued to feel well after the diabetic condition was brought under control and felt well until May 1932 when she complained of pain in her chest, weakness, loss of ten pounds weight and of a generally run-down condition. She was admitted to

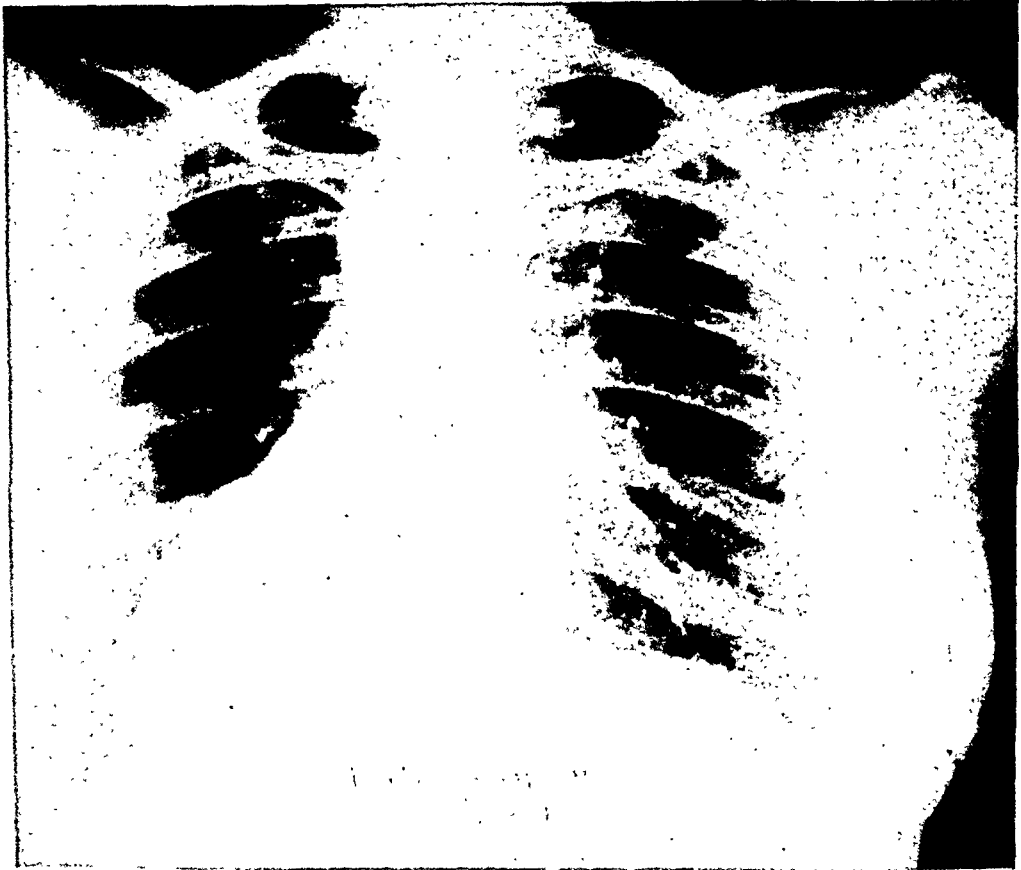


FIG. 5. Case V, May 1931.

lung fields, slightly more in the right than the left. The appearance is suggestive of infection of the lungs, possibly tuberculosis." (Figure 5). Physical examination and sputum were negative. The patient remained in bed all summer under the care of her family physician who completely disregarded the diabetic condition and gave her a high calory diet without insulin. She returned to the clinic in December 1931 with marked glycosuria and a fasting blood sugar of 250 mg. per 100 c.c. She had lost nine pounds in weight; we attributed this loss to the uncontrolled diabetes. Roentgen-ray at that time was reported as follows: "Examination of the chest shows some in-

the tuberculosis ward of the Charles V. Chapin Hospital and was discharged from there June 1, 1932, with the diagnosis of healed tuberculosis. She has remained in good condition since then.

SUMMARY AND CONCLUSIONS

1. In our clinic comprising 500 active diabetic patients, 408, or 81.6 per cent, unselected cases have had roentgen-ray examination of the lungs.

2. Five, or 1.2 per cent, showed positive roentgen-ray evidence of tuberculosis.

3. The prognosis in one case is unfavorable or uncertain, but in the remaining four it is good.

4. It is of interest to note that none of our active cases has shown the serious type of tuberculosis described by Sosman and Steidl.

5. The incidence of tuberculosis in our group corresponds closely to that noted in other recently published statistics.

6. All of our cases of active tuber-

culosis seen since this study was undertaken are alive. The longest duration of the tuberculous infection in this group is three years and ten months.

7. In our experience tuberculosis has not occurred any more frequently in diabetics than in non-diabetics. In those cases in whom tuberculosis has developed it has not run a more unfavorable course than in non-diabetics.

BIBLIOGRAPHY

¹JOSLIN, E. P.: The treatment of diabetes mellitus, 1923, Lea and Febiger, Philadelphia.

²MONTGOMERY, C. M.: Diabetes mellitus and tuberculosis, *Am. Jr. Med. Sci.*, 1912, cxliv, 543-561.

³BOSWELL, H.: Diabetes and tuberculosis, *New Orleans Med. and Surg. Jr.*, 1927, lxxix, 668-669.

⁴MUSSER, J. H., JR.: Diabetes and tuberculosis, *Med. Clin. North Am.*, 1924, viii, 771-774.

⁵GRIESINGER, quoted by BOSWELL, H.: Diabetes and tuberculosis, *New Orleans Med. and Surg. Jr.*, 1927, lxxix, 668-669.

⁶WINDLE, quoted by BOSWELL, H.: *Loc. cit.*

⁷FITZ, R.: The problem of pulmonary tuberculosis in patients with diabetes, *Am. Jr. Med. Sci.*, 1930, clxxx, 192-200.

⁸FITZ, R., and MURPHY, W. P.: The cause of death in diabetes mellitus, *Am. Jr. Med. Sci.*, 1924, clxviii, 313-325.

⁹SOSMAN, M. C., and STEIDL, J. H.: "Diabetic tuberculosis", *Am. Jr. Roentgenol.*, 1927, xvii, 625-629.

¹⁰ADAMS, S. F.: Complications of diabetes: a study of the incidence of and mortality from tuberculosis, acidosis, and gangrene in one thousand cases of diabetes, *Proc. Staff Meet., Mayo Clinic*, 1929, iv, 192.

Primary Hypochromic Anemia*

Its Importance in Medical and Surgical Diagnosis

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HYPOCHROMIC anemia in adults is generally considered as secondary to some other disease process, such as hemorrhage, malignancy, infection, or nephritis. This view has prevailed so long that "hypochromic anemia" and "secondary anemia" are often used as synonymous terms. In recent years, however, a type of hypochromic anemia has been recognized as an independent disease. The condition may be referred to as primary hypochromic anemia. It occurs almost exclusively in women. Achlorhydria is nearly always present. One of the most characteristic features of the disease is a rapid, almost dramatic, response to iron therapy in massive doses. Its recognition is of great importance, not only because it requires a specific type of therapy, but also because of the possibility of its confusion with anemia due to chronic hemorrhage. The common assumption that a "cause" must be found for every case of hypochromic anemia is erroneous and may lead to ineffective treatment.

Textbooks of medicine contain no description of primary hypochromic anemia. Likewise, the special treatises on hematology do not describe it, ex-

cept that Naegli¹ gives a short account of its essential features, calling it "chronic chlorosis". Knud Faber² accurately described the disease in 1913. Recent interest, however, dates from the paper published in 1929 by Kaznelson, Reimann, and Weiner.³ They refer to it as achylic chloranemia. Other terms that have been used are chronic hypochromic anemia (Altschuller⁴), chlorotic anemia with achlorhydria (McCann and Dye⁵), achylic anemia (Schulten⁶), essential hypochromic anemia (Schulten⁷), hypochromic anemia with achlorhydria (Waugh⁸), idiopathic hypochromemia (Mills⁹), idiopathic secondary anemia (Watkins¹⁰), chronic chlorosis and chlorotic anemia (Mettier and Minot¹¹), chronic microcytic anemia (Witts¹²). I prefer the term primary hypochromic anemia as introduced by Dame-shek.¹³ The condition is obviously not chlorosis. The age distribution is entirely different. Moreover, chlorosis was frequently accompanied by hyperacidity. The hyperacidity was sometimes so marked in chlorosis that the possibility of an accompanying peptic ulcer was considered (Rosenow¹⁴).

I have recently encountered four patients with primary hypochromic anemia. The case histories of two of them are below.

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CASE I

C. M., female, aged 41, ambulant, first seen January 24, 1931, complaining of general weakness. Her general health had been good prior to the present illness. There had been two attacks of influenza, eleven and two years ago respectively. The patient had been married for twenty years. One child was living and well. The menses were regular, lasted three to four days, and were described as being profuse.

The onset of the present illness had been gradual. About three years ago she began to tire easily. This had increased, until recently any exertion caused shortness of breath. The tongue had become markedly sore, off and on during the illness. There had been aching in both thighs extending to the knees. The appetite had been good. Patient stated she had been told that all of her trouble was due to excessive loss of blood at the menstrual periods and that no improvement could be expected without an operation to correct this abnormality.

Examination showed a pale, middle-aged woman, 63 inches high and weighing 129 pounds. The sclerae were clear. The tongue was smooth, red, and showed a few superficial ulcerations at the margins. The general physical examination revealed no abnormality. The liver and spleen were not palpable. The reflexes were normal. The vibratory sense was not impaired. The uterus was retroverted, otherwise there was no pelvic abnormality. Fluoroscopic examination of the heart, lungs, and stomach showed no abnormality.

Laboratory Examination: Blood hemoglobin, 48 per cent (Newcomer-Klett glass standard, 15.3 gms. per 100 c.c. being considered 100 per cent); red blood cells, 3,520,000 per cubic millimeter; color index, 0.7; white blood cells, 5,550 per cubic millimeter; neutrophils, 62 per cent; eosinophiles 4 per cent; basophiles, 1 per cent; lymphocytes, 30 per cent; monocytes, 3 per cent. There was moderate poikilocytosis and anisocytosis, microcytes being especially numerous. The red blood cells were obviously hypochromic. There was no evident abnormality of the platelets. On two examinations there was no free hydrochloric acid in the gastric contents after an Ewald meal, and

the total acidity was 11 per cent. There was no lactic acid nor occult blood. The urine contained no urobilinogen (Ehrlich's aldehyde reagent) and was otherwise normal. There was no occult blood in the stools and no parasites nor ova. The blood serum was pale; icterus index six. The Wassermann reaction was negative.

The patient was given nine Blaud's pills (U. S. P.) a day and forty drops of dilute hydrochloric acid after each meal. In addition, a diet was prescribed which included fresh lean meat, green vegetables, cooked fruit, and fresh fruit each day.

The hemoglobin increased to 83 per cent in four weeks and to 90 per cent in six weeks. The symptoms disappeared entirely. The pills were then reduced to three a day, but the patient, against advice, left them off entirely. After three months without iron, the hemoglobin had decreased to 70 per cent. The pills were then resumed, nine a day. At the end of four additional months the hemoglobin was 111 per cent. Four months later she had again relapsed, hemoglobin 73 per cent. Patient stated that she saw no need of regular visits for hemoglobin determinations and dosage adjustment, for she had learned when to take iron merely from her subjective sensations.

CASE II

C. H., female, age 40, ambulant, was first seen March 3, 1932, complaining of stomach trouble and prolonged slight elevation of temperature. The patient had been married twelve years; there had been no pregnancies. Four years before an operation had been performed for the removal of an ovarian tumor. The past history had otherwise been uneventful.

The patient attributes the onset of the present illness to an attack of influenza two years ago. Since then she has had frequent afternoon elevation of temperature reaching from 99½ degrees to 100½ degrees. This has led to her supervision as a tuberculosis suspect. She has gradually developed marked shortness of breath. She has vomited frequently on slight provocation. There is an almost constant feeling of discomfort in the epigastrium, amounting almost to pain. Abdominal flatulence has been marked. There

have been two recent attacks of diarrhea. The patient has lost her appetite for meat and has eaten very little meat during the past three years. The menses are regular and profuse.

Examination: The patient was an extremely pallid woman; weight 111 pounds and height 62 inches. The tongue was smooth and pale. The general physical examination revealed no abnormality. The pelvic organs were normal. Reflexes were normal; vibration well perceived. Fluoroscopic examination of heart, lungs and stomach showed no abnormality. Electrocardiograph was normal.

Laboratory Examination: Hemoglobin, 30 per cent; red blood cells, 2,670,000 per cubic millimeter; color index 0.6; white blood cells 2,800 per cubic millimeter; neutrophils, 56 per cent; basophiles, 1 per cent; lymphocytes, 20 per cent; monocytes, 9 per cent. One normoblast seen in counting 100 leukocytes. Slight poikilocytosis was present, and marked anisocytosis with microcytes predominating. Marked hypochromia. The platelets appear normal. Gastric contents: no free hydrochloric acid; total acidity, 6 per cent; no blood or lactic acid. Icterus index, 6. The urine contained no albumin, sugar, casts, or urobilinogen. There was no occult blood, nor any parasites or ova in the stools. The Wassermann and Kahn reactions were negative.

Exactly the same treatment was given as in Case I, except that the Bland's pills were increased to 12 a day. Three weeks later the hemoglobin was 60 per cent; after six weeks it was 80 per cent, and after nine weeks, 93 per cent. The leukocytes never increased above 4,000. There was no further gastric distress or fever after the hemoglobin reached 60 per cent.

The other two patients were also women, aged 35 and 38 years respectively. Both had achlorhydria. The hemoglobin of one was 60 per cent, and of the other 63 per cent. Both improved rapidly on 9 Bland's pills a day.

ETIOLOGY

The etiology of the condition is obscure. It is probable that the achlorhydria and the anemia are both the result of a constitutional defect, rather than that the anemia is a result of the achlorhydria. Dameshek¹⁸ suggests that the disease is possibly related to the deficient gastric digestion of organic iron. Many of these patients, like Case II above, give a history of eating very little meat. This aversion, however, may be a simple result of the achlorhydria, and is not necessarily concerned in the etiology of the condition. Certainly, large quantities of meat in the form of liver, as used in the treatment of pernicious anemia, have no influence on the condition.

Although primary hypochromic anemia and pernicious anemia have dissimilar blood pictures and require entirely different types of therapy, there appears to be a link between the two diseases. Schulten calls attention to the fact that primary hypochromic anemia and pernicious anemia may occur in different members of the same family. He also cites from the literature two instances of individuals with primary hypochromic anemia who later developed pernicious anemia. Dameshek has seen a similar change from one type to the other.

One of the most surprising features of this newly recognized disease is its great incidence. It is unquestionably far more common than pernicious anemia. Wits estimates that among every 100 persons with achlorhydria, there will be 20 individuals with primary hypochromic anemia and 10 with pernicious anemia. My own four cases were encountered among 250 consecu-

tive ambulant patients. Among these patients there was not a single case of pernicious anemia. While women greatly predominate, men are not immune to primary hypochromic anemia. One of the seven cases reported by Dameshek was a man. Fourteen per cent of the 117 cases studied by Witts¹² were in men.

About half the cases occur between the ages of 30 and 42 years. The disease becomes much less frequent after the menopause, although it does not disappear entirely. One of the Mills⁹ patients was 58 years old, and another 61. Strauss¹⁵ has observed three instances in pregnancy. Mills believes that pregnancy is merely a complication of the disease and does not play any part in its etiology.

SYMPTOMS

The symptoms consist as a rule of the usual symptoms of anemia, namely, shortness of breath, palpitation, weakness and dizziness. These symptoms are sometimes surprisingly slight considering the degree of anemia. In addition, there may be numbness and tingling of the extremities. Gastric complaints, such as loss of appetite, and diarrhea are frequent. Many of the patients give a history of profuse menstrual periods. Long continued low fever may occur, as in pernicious anemia. This fever may cause tuberculosis to be suspected, as in Case II above. Aching in the limbs and joints is frequent.

EXAMINATION

The patients appear very pale. The pallor, often alabastrine, contrasts with the yellowish tint of pernicious anemia.

The tongue is red in a large proportion of the cases. Typical Hunterian glossitis may be present. Koilonychia (spoon-shaped nails) is often marked. The spleen is sometimes palpable. Achlorhydria is present in almost all of the patients, though the finding is not as absolute as in pernicious anemia. Dameshek has noted postero-lateral sclerosis, though this is rare.

The hemoglobin may be as low as 15 per cent (Dameshek¹³). The color index is much below 1.0, but the red cells are as a rule more reduced than in the figures given for chlorosis. Microcytes predominate. This is obvious not only from the examination of the smear, but has been shown by careful measurements of the diameters of the red cells by McCann and Dye⁵ and by Schulten.⁷ There is considerable poikilocytosis and anisocytosis. Nucleated red cells are rare. Leukopenia is present as a rule. The icterus index is low, and the urine contains no more than a trace of urobilin, if any.

DIAGNOSIS

The blood picture of primary hypochromic anemia sharply separates it from pernicious anemia. Unlike pernicious anemia, however, the blood picture of primary hypochromic anemia is not pathognomonic. Knowledge of the primary form of hypochromic anemia in no way eliminates the necessity of a very thorough examination for known causes of secondary hypochromic anemia, such as infections, nephritis, occult malignancy, or occult hemorrhage. The leukopenia helps to rule out subacute bacterial endocarditis. The stools should invariably be examined for occult blood, and roentgenological

examination of the gastrointestinal tract is desirable. Achlorhydria helps to establish the diagnosis of primary hypochromic anemia if there is no reason to suspect gastric carcinoma. Failure to improve under proper treatment should cause early splenic anemia to be suspected.

The greatest difficulty lies in distinguishing between primary hypochromic anemia and the anemia of menorrhagia, particularly since profuse menstrual periods may occur in the former disease. If there is no obvious gynecological lesion, operation or roentgen-ray sterilization should certainly be delayed until after a therapeutic test with iron, since such a test at the most requires only four to six weeks. In my opinion, some of the anemias attributed to functional menorrhagia and submitted to roentgen-ray sterilization are in reality instances of primary hypochromic anemia. This error is all the more common on account of the prevalent belief already mentioned that hypochromic anemia is always secondary to some other process such as hemorrhage. Likewise, recognition of this disease renders caution necessary in attributing anemia to doubtful bleeding from hemorrhoids.

TREATMENT

The essential feature of treatment is the use of iron in large doses. The usual small doses of iron are without effect. The form of the iron is immaterial, if the dosage is large enough. There are three forms in use, any one of which is satisfactory.

1. Bland's pills, U.S.P. The dose is 9 to 12 five-grain pills a day. The

pills should be freshly prepared so as to guard against failure of disintegration. (Each pill contains 30 mg. of Fe as FeCO_3). Vallet's mass, U.S.P. (17 per cent Fe as FeCO_3), may also be used in doses of 60 grains a day.

2. Iron and ammonium citrate, U.S.P. (17 per cent Fe), is an inexpensive preparation. It can be easily prescribed in 25 per cent aqueous solution, and given diluted in milk or water in the dosage of two drams of this solution three times a day. To prevent any possibility of diarrhea, Minot and Castle recommend beginning with one-half dram doses and increasing to two drams three times a day.

3. Reduced iron is the favorite preparation in Germany.⁷ It is given in doses of 6 to 10 grams daily.

It is useless to give proprietary preparations of iron and it is needless to give iron by injections.

There is some difference of opinion as to whether copper enhances the effect of the iron. Mills⁹ is of the opinion that it does, and he gave daily 1/16 grain of copper carbonate (2.1 mg. Cu) in 90 grains of Bland's mass. One of the patients observed by Dameshek likewise failed to show satisfactory improvement until a daily dose of 0.1 gram copper sulfate (23 mg. Cu) was added to the iron. The other six cases observed by Dameshek¹³ improved satisfactorily on iron alone.

Considerable weight must be given to the findings of Mills. His observations were apparently well controlled. Five of his patients were kept for many months on 60 grains of Bland's mass daily, without improvement. Prompt improvement occurred when

copper was added. Witts,¹² however, is emphatic in his belief that copper plays no part in the improvement, for the iron preparation used by him was practically free of copper, containing only 0.01 mg. of Cu in the daily dose. This quantity of copper is less than that in the ordinary diet. The Bland's pills used by me were likewise prepared from a very pure form of ferrous sulfate (Merck, granular, U.S.P., X), the daily dose of 12 pills containing only 0.1 mg. Cu. The iron preparation used by McCann and Dye contained 0.36 mg. Cu in the daily dose.

It appears then that improvement in most instances is satisfactory without the addition of copper. Whether the improvement will be accelerated by the addition of copper requires more study before being accepted as a proved fact. So far, there has been no evidence that arsenic is an aid in this type of anemia.

In addition to iron, I gave my patients hydrochloric acid, principally on account of the evidence presented by Mettier and Minot¹¹ that iron is better absorbed from an acid medium. This addition does not seem to be essential, though it will have the same effect in relieving gastric symptoms as in achlorhydria from other causes.

The iron therapy must be continued in full dose until the hemoglobin reaches 85 per cent to 90 per cent. Then the dose may be reduced to about one-fourth of the previous amount. This dosage must be continued indefinitely in order to prevent relapse, unless the patient can report for hemoglobin estimations every few months. A marked tendency toward relapse is one of the features of the disease. Some of these patients finally learn

themselves to know when they need iron.

Minot and Castle¹⁶ call attention to the fact that the best results are obtained when patients receive a proper diet as well as specific therapy. Such a diet will include fresh and cooked fruits, green vegetables and ample animal proteins, particularly meat.

As a rule, six to eight weeks of intensive iron therapy is required to bring the hemoglobin up to 85 per cent or 90 per cent. My cases required about 40 days for the hemoglobin to increase to 85 per cent or 90 per cent. Dameshek¹⁸ reported a case with an initial hemoglobin of 15 per cent which increased to 77 per cent in seven weeks, and to 88 per cent after an additional seven weeks.

SUMMARY

Primary hypochromic anemia is an independent disease entity occurring principally in women between the ages of 30 and 42 years. Achlorhydria is almost always present. The blood findings are in no essential way different from those in anemia resulting from malignancy, infection, nephritis, or chronic hemorrhage. A thorough search for such well established causes of hypochromic anemia should always be made. Knowledge of primary hypochromic anemia should, however, prevent a hasty attribution of anemia to such causes as functional menorrhagia or hemorrhoids. In case of doubt, the patient should be submitted to therapeutic test before radical procedures are performed.

One of the most characteristic features of the disease is a rapid thera-

examination of the gastrointestinal tract is desirable. Achlorhydria helps to establish the diagnosis of primary hypochromic anemia if there is no reason to suspect gastric carcinoma. Failure to improve under proper treatment should cause early splenic anemia to be suspected.

The greatest difficulty lies in distinguishing between primary hypochromic anemia and the anemia of menorrhagia, particularly since profuse menstrual periods may occur in the former disease. If there is no obvious gynecological lesion, operation or roentgen-ray sterilization should certainly be delayed until after a therapeutic test with iron, since such a test at the most requires only four to six weeks. In my opinion, some of the anemias attributed to functional menorrhagia and submitted to roentgen-ray sterilization are in reality instances of primary hypochromic anemia. This error is all the more common on account of the prevalent belief already mentioned that hypochromic anemia is always secondary to some other process such as hemorrhage. Likewise, recognition of this disease renders caution necessary in attributing anemia to doubtful bleeding from hemorrhoids.

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1. Blaud's pills, U.S.P. The dose is 9 to 12 five-grain pills a day. The

pills should be freshly prepared so as to guard against failure of disintegration. (Each pill contains 30 mg. of Fe as FeCO_3). Vallet's mass, U.S.P. (17 per cent Fe as FeCO_3), may also be used in doses of 60 grains a day.

2. Iron and ammonium citrate, U.S.P. (17 per cent Fe), is an inexpensive preparation. It can be easily prescribed in 25 per cent aqueous solution, and given diluted in milk or water in the dosage of two drams of this solution three times a day. To prevent any possibility of diarrhea, Minot and Castle recommend beginning with one-half dram doses and increasing to two drams three times a day.

3. Reduced iron is the favorite preparation in Germany.⁷ It is given in doses of 6 to 10 grams daily.

It is useless to give proprietary preparations of iron and it is needless to give iron by injections.

There is some difference of opinion as to whether copper enhances the effect of the iron. Mills⁹ is of the opinion that it does, and he gave daily 1/16 grain of copper carbonate (2.1 mg. Cu) in 90 grains of Blaud's mass. One of the patients observed by Dameshek likewise failed to show satisfactory improvement until a daily dose of 0.1 gram copper sulfate (23 mg. Cu) was added to the iron. The other six cases observed by Dameshek¹³ improved satisfactorily on iron alone.

Considerable weight must be given to the findings of Mills. His observations were apparently well controlled. Five of his patients were kept for many months on 60 grains of Blaud's mass daily, without improvement. Prompt improvement occurred when

copper was added. Witts,¹² however, is emphatic in his belief that copper plays no part in the improvement, for the iron preparation used by him was practically free of copper, containing only 0.01 mg. of Cu in the daily dose. This quantity of copper is less than that in the ordinary diet. The Bland's pills used by me were likewise prepared from a very pure form of ferrous sulfate (Merck, granular, U.S.P., X), the daily dose of 12 pills containing only 0.1 mg. Cu. The iron preparation used by McCann and Dye contained 0.36 mg. Cu in the daily dose.

It appears then that improvement in most instances is satisfactory without the addition of copper. Whether the improvement will be accelerated by the addition of copper requires more study before being accepted as a proved fact. So far, there has been no evidence that arsenic is an aid in this type of anemia.

In addition to iron, I gave my patients hydrochloric acid, principally on account of the evidence presented by Mettier and Minot¹¹ that iron is better absorbed from an acid medium. This addition does not seem to be essential, though it will have the same effect in relieving gastric symptoms as in achlorhydria from other causes.

The iron therapy must be continued in full dose until the hemoglobin reaches 85 per cent to 90 per cent. Then the dose may be reduced to about one-fourth of the previous amount. This dosage must be continued indefinitely in order to prevent relapse, unless the patient can report for hemoglobin estimations every few months. A marked tendency toward relapse is one of the features of the disease. Some of these patients finally learn

themselves to know when they need iron.

Minot and Castle¹⁶ call attention to the fact that the best results are obtained when patients receive a proper diet as well as specific therapy. Such a diet will include fresh and cooked fruits, green vegetables and ample animal proteins, particularly meat.

As a rule, six to eight weeks of intensive iron therapy is required to bring the hemoglobin up to 85 per cent or 90 per cent. My cases required about 40 days for the hemoglobin to increase to 85 per cent or 90 per cent. Dameshek¹³ reported a case with an initial hemoglobin of 15 per cent which increased to 77 per cent in seven weeks, and to 88 per cent after an additional seven weeks.

SUMMARY

Primary hypochromic anemia is an independent disease entity occurring principally in women between the ages of 30 and 42 years. Achlorhydria is almost always present. The blood findings are in no essential way different from those in anemia resulting from malignancy, infection, nephritis, or chronic hemorrhage. A thorough search for such well established causes of hypochromic anemia should always be made. Knowledge of primary hypochromic anemia should, however, prevent a hasty attribution of anemia to such causes as functional menorrhagia or hemorrhoids. In case of doubt, the patient should be submitted to therapeutic test before radical procedures are performed.

One of the most characteristic features of the disease is a rapid thera-

peutic response to large amounts of iron by mouth, such as daily doses of 4 grams of Bland's pills, or 6 grams of ferric and ammonium citrate, or 6

grams of reduced iron. Small doses of iron are not effective. The patients should be kept under close supervision since relapses are frequent.

REFERENCES

- ¹NAEGLI, O.: *Blutkrankheiten und Blutdiagnostik: Lehrbuch der klinischen Hämatologie*, 5th ed., 1931, J. Springer, Berlin.
- ²FABER, K.: *Anämische Zustände bei der chronischen Achylia gastrica*, Berl. klin. Wchnschr., 1913, 1, 958.
- ³KAZNELSON, P., REIMANN, F., and WEINER, W.: *Achylische Chloranämie*, Klin. Wchnschr., 1929, viii, 1071-1074.
- ⁴ALTSCHULLER, G.: *Sur le pathogénie de l'anémie hypochrome chronique, dite achylique à propos d'une observation personnelle*, Acta med. Scandinav., 1929, lxx, 119-138.
- ⁵MCCANN, W. S., and DYE, J.: *Chlorotic anemia with achlorhydria, splenomegaly, and small corpuscular diameters*, ANN. INT. MED., 1931, iv, 918-930.
- ⁶SCHULTEN, H.: *Zur Behandlung hypochromer Anämien mit maximalen Eisendosen*, Münch. med. Wchnschr., 1930, lxxii, 355-356.
- ⁷SCHULTEN, H.: *Über die essentielle hypochrome Anämie (achylische Chloranämie) und ihre Beziehungen zur perniziösen Anämie*, Münch. med. Wchnschr., 1932, lxxix, 665-667.
- ⁸WAUGH, T. R.: *Hypochromic anemia with achlorhydria*, Arch. Int. Med., 1931, xlvii, 71-81.
- ⁹MILLS, E. S.: *Idiopathic hypochromemia*, Am. Jr. Med. Sci., 1931, clxxxii, 554-565.
- ¹⁰WATKINS, C. H.: *A classification of chronic idiopathic secondary anemia, with special reference to morphology of blood*, Jr. Am. Med. Assoc., 1929, xciii, 1365-1367.
- ¹¹METTIER, S. R., and MINOT, G. R.: *The effect of iron on blood formation as influenced by changing the acidity of the gastroduodenal contents in certain cases of anemia*, Am. Jr. Med. Sci., 1931, clxxxii, 25-36.
- ¹²WITTS, L. J.: *Chronic microcytic anemia*, Brit. Med. Jr., 1931, ii, 883, 888.
- ¹³DAMESHEK, W.: *Primary hypochromic anemia (erythro-normoblastic anemia); a new type of idiopathic anemia*, Am. Jr. Med. Sci., 1931, clxxxii, 520-553.
- ¹⁴ROSENOW, G.: *Blutkrankheiten*, 1925, Julius Springer, Berlin.
- ¹⁵STRAUSS, M. B.: *Chlorotic anemia of pregnancy, report of 3 cases*, Am. Jr. Med. Sci., 1930, clxxx, 818-823.
- ¹⁶MINOT, G. R., and CASTLE, W. B.: *The adequate treatment of anemia*, ANN. INT. MED., 1931, v, 159-169.

The Effect of Liver Therapy on the Neurologic Aspects of Pernicious Anemia*†

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THE treatment of pernicious anemia with liver, introduced by Minot and Murphy¹ in 1926, after the experimental work of Whipple and his associates, has had a remarkable effect on the clinical course of the disease. The response of the nervous manifestations has been discussed by various authors with considerable difference of opinion. This is due partly to the use of different criteria in evaluating the results of treatment. Some observers have relied on improvement of symptoms not necessarily dependent upon structural restoration, while others have based their conclusions on the rigid interpretation of abnormal neurologic signs. Another cause for confusion is the presentation of one or several improved cases, with the exclusion of less favorable ones. A survey of reports of this type may lead to an unwarranted degree of optimism.

It is the purpose of this paper to present the results of a study of 47 cases of pernicious anemia admitted to the Strong Memorial and Rochester

Municipal Hospitals since the opening of these institutions in 1926. The diagnoses were established by the usual criteria. Only those cases were included in which adequate follow-up examinations were made.

The treatment consisted of the daily administration of liver or liver extract by mouth without significant periods of interruption. The average duration of treatment in the entire series was 25 months. One of the patients first took liver in 1924 upon the suggestion of Dr. Joseph Roby of Rochester as the result of the experimental work of Whipple. Another patient has been taking desiccated hog's stomach instead of a preparation of liver. As the result obtained in this case is similar to those observed in the remainder of the series, we have included it with the rest. Patients with severe neurologic symptoms received brewer's yeast and cod liver oil in addition to liver therapy. This was suggested by the case report by Conner² and later by the experimental work of Castle³ and of Mellanby.⁴ Approximately half of the patients took dilute hydrochloric acid.

Of the total of 47 cases, 29 presented both symptoms and signs of spinal cord degeneration, 10 had symptoms but no

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signs of nervous system involvement, and three had no indication of this complication. The remaining five patients had prominent psychic disorders and are considered solely from this aspect; their period of observation was too short to judge the effect of liver on their cord symptoms. In 40 patients, treatment was regular and uninterrupted; this was adequate in 25 cases, as indicated by a consistent maintenance of the blood level at four million or more red blood cells per cubic millimeter; in the remaining 15 cases, the average blood count was below this level, usually due to an inadequate intake of liver preparations.

RESULTS OF LIVER THERAPY

In the evaluation of the therapeutic results obtained by the use of liver, two criteria must be employed. First, and perhaps most important from a clinical standpoint, is the degree of symptomatic relief expressed by the comfort and rehabilitation of the patient. Second, progress or regression of the degenerative process in the nervous system must be measured by signs which depend solely upon structural change within that system.

It is a generally accepted fact that certain nervous symptoms respond favorably in a majority of patients. Most notable among these are paresthesia and ataxia. In 24 of the adequately treated patients who complained of paresthesias, 14 reported that this symptom improved or disappeared. It remained unchanged in four. In six of the patients the paresthesias became more severe, in parallel with signs of a steady progression of the cord degeneration. In the poorly

treated group the proportion of patients whose paresthesias improved is smaller. It is interesting that one of the patients described the replacement of soreness of the tongue by a disagreeable sensation of numbness.

Ataxia was a prominent feature in 14 of the well treated cases. In six of these cases there was improvement in this symptom. In some instances the amelioration was striking, in four ataxia became definitely worse, and in four others it was unchanged. Of four inadequately treated patients the ataxia improved in one, and remained stationary or progressed in three.

In gross contrast to the fairly favorable influence of treatment on symptoms, the objective examination of the nervous system in our series indicated a progression of the cord degeneration in 10 of 17 well treated cases. All but one of these showed extension of the process to the lateral columns. The course in patients with blood counts above five million did not differ from that in the others of this group. In six of the cases the abnormal signs remained unchanged. Demonstrable improvement occurred in only one case in which there was a return of joint sensibility without return of perception of vibration or change in reflexes. Of 10 patients who received inadequate treatment the signs progressed in eight and remained stationary in two. One patient of this group developed paraplegia in flexion, a condition described in this disease by Hall and Hirsch.⁵

The possibility of the prevention of cord degeneration by the use of liver is supported by our data. At the time of the original examination the neurologic findings were normal in 19 pa-

tients. Of the nine who were satisfactorily treated, only one developed pathologic signs, while this occurred in five of the ten poorly treated patients.

The following case illustrates progression of cord degeneration under treatment.

CASE I

L.G., male, aged 63, was referred by Dr. C. P. Thomas for a neurological examination, November 12, 1929. He complained of mental depression and of numbness and tingling in the hands and feet. The family history is of unusual interest in that his brother, R. G., aged 58, died three months previously of a progressive cord degeneration associated with pernicious anemia. R.G. was first examined by one of us when his symptoms were identical with those of his brother; liver treatment was instituted at this time.

The present illness of L. G. began five months previously with mild mental depression. This was accompanied after two months by persistent paresthesias in the hands and feet and impairment of skilled movements of the hands. There was no disturbance of the gait. Slight soreness of the tongue had been present at times.

On examination, the patient was a well nourished man of ruddy complexion. He was mentally clear. The expression and general behavior indicated considerable anxiety. The neurologic examination was negative except for slight awkwardness in buttoning the clothes. This was the only evidence of incoördination. Detailed examination of deep sensibility revealed no abnormalities in either the upper or lower extremities. The tendon reflexes, plantar reflex, gait and station were all normal.

The general physical examination was negative except for slight papillary atrophy of the tongue.

The laboratory findings were: Blood hemoglobin 86 per cent; red blood cells 4,500,000 per cubic millimeter; white blood cells 6,000 per cubic millimeter. The blood smear at the time of this examination was not definitely abnormal. A gastric analysis revealed the absence of free hydrochloric

acid in the fasting specimen and also in those taken after the test meal. The urine and stool examinations were negative. The cerebrospinal fluid was normal. The blood and spinal fluid Wassermann tests were negative.

The diagnosis was pernicious anemia with early subacute combined degeneration. Liver treatment and diet rich in vitamins were instituted. The patient was again seen on May 22, 1931. He complained of weakness of the legs, difficulty in walking, girdle sensation and constipation; these symptoms had developed since the preceding fall. The paresthesias were more severe. The examination showed increased tendon reflexes in the upper extremities with a bilateral Hoffmann sign. The legs were weak but he was able to walk unassisted though with an ataxic gait. The knee jerks were present and about normal. The Achilles reflexes were lost. A Babinski sign was present on the left. Position sense of the toes was greatly impaired and vibratory sensation was lost over the bony prominences of the pelvis and lower extremities. He was unable to stand in the Romberg position without falling.

His condition has progressed further so that at the present time he is unable to walk unless assisted by two persons. The ataxia of the hands has become more marked and he is unable to write. Paresthesias likewise have increased.

Since November 1929 he has taken six vials of liver extract daily and also fresh liver twice a week without interruption. Blood counts were done at intervals of a month. The hemoglobin has varied between 95 and 110 per cent; the average red blood cell count was 4.1 million per cubic millimeter. The color index has been persistently over 1.0 and the smears have shown definite anisocytosis and poikilocytosis.

COMMENT

In this case the diagnosis was made shortly after the onset of nervous symptoms and before the characteristic blood picture of pernicious anemia had developed. Treatment was started before objective evidence of cord degeneration was present except

for impairment of skilled movements of the hands. The patient appreciated the similarity of his condition to that of his deceased brother and realized the necessity for continuous treatment. In spite of this the course was slowly but steadily progressive.

The improvement of ataxia under liver therapy has been noted. Most authors are agreed that the favorable response of this symptom is not usually paralleled by improvement of deep sensibility. In fact, the ataxia may at times improve in the face of actual progression of the spinal cord lesion as evidenced by increasing sensory and motor disturbances. Analysis of our series shows that deep sensibility returned in only one of the six patients in whom ataxia improved. Improvement in strength and muscle re-education, as suggested by many authors, are probably important in the correction of this symptom.

CASE II

M. N., a housewife, aged 56, was admitted to the Strong Memorial Hospital October 22, 1929 and discharged four days later. She complained chiefly of numbness and tingling of the hands and feet. The past and family histories were irrelevant. The present illness began two years previously with extreme weakness. She was confined to bed for three weeks with gradual but not complete return of strength. A short time later she complained of a sensation of swelling of the legs which was slowly replaced by a feeling of numbness and tingling below the knees. In December 1928 numbness and tingling of the hands and soreness of the tongue became troublesome symptoms. For six months prior to entry she had been unaware of the position of her feet and had been unable to walk or stand unless assisted.

Examination: Mentally clear. The skin and mucous membranes had good color. The tongue was very red and sore, and

there was slight atrophy of the papillae along the edges. The cranial nerves were normal. The strength of the upper extremities was fairly good. The tendon reflexes in the upper extremities were not elicited. There was a considerable degree of ataxia with both hands, by the finger to nose test. Vibratory sensation was diminished over the wrists. Sense of motion and position of the fingers was lost in one hand (presumably the right). The knee and Achilles reflexes were absent. The plantar response was flexion on both sides. There was loss of sense of motion and of position of the feet and toes. Vibratory sensation was lost over the bony prominences of the pelvis and lower extremities. The legs were extremely ataxic. Examination of superficial sensibility showed a diminution of tactile and thermal sensation below the knees. The general physical examination was negative. The laboratory findings were: Blood hemoglobin 86 per cent; red blood cells 3,590,000 per cubic millimeter; white blood cells 8,600 per cubic millimeter. The differential count was as follows: Polymorphonuclear neutrophils 67 per cent; large and small lymphocytes 26 per cent; large mononuclears and transitionals 5 per cent; eosinophiles 1 per cent; basophiles 1 per cent. In the smear the red blood cells were large and stained deeply. There were moderate variations in size and shape. The platelets were normal. The chemical examination of the blood plasma showed non-protein-nitrogen 24 mg. per 100 c.c., sugar 74.9 mg. per 100 c.c.; icterus index 8. A gastric analysis revealed the absence of free hydrochloric acid in both the fasting specimen and in those taken after the test meal. Urine examination: clear; acid; sp. gr. 1.015; albumin 0; sugar 0; urobilin 0; micro, occasional cast and 10-14 white blood cells per high power field. The cerebrospinal fluid was clear; pressure 125 millimeters of water; normal dynamics; 4 cells per cubic millimeter; Pandy test negative; gold sol curve 0001100000. The blood and spinal fluid Wassermann tests were negative.

The diagnosis was pernicious anemia with subacute combined degeneration of the cord. The patient was advised to take liver, high

vitamin diet and was instructed regarding Fraenkel exercises.

After leaving the hospital the patient took uncooked fetal calves' liver for a period of four weeks. Three weeks after starting treatment she stated that, whereas previously she was unaware of the position of her lower extremities, "feeling" had returned. In May 1931 she was able to walk with the aid of a cane and in September she was able to get along without a cane, climb stairs and do her housework. The numbness and tingling of the lower forearms, hands, legs, and feet persisted and became even more marked in the upper extremities. She was unable to pick up or hold small objects with the hands. The soreness of the mouth completely disappeared under treatment.

The treatment consisted of uncooked fetal calves' liver, about three and one-half pounds per week, for a period of four weeks. The same amount of uncooked calves' liver was then taken for a period of six months and since then she has taken one vial of liver extract three times a day. She has also taken considerable amounts of cod liver oil which she thinks has been a factor in her general improvement. In addition to the medical treatment, systematic muscle coordination exercises were employed.

Neurological Examination: December 1931. Her general health was excellent and there was no evidence of anemia. The cranial nerves were normal. The strength of the upper extremities was very good. The biceps and triceps reflexes were present but diminished. Hoffmann's thumb sign was absent. There was no ataxia by the finger to nose test except of the right hand when the eyes were closed. Vibratory sensation was diminished over the wrists, especially the right. Sense of motion and position of the fingers was present in the left hand and absent on the right. The knee jerks were increased on both sides. The Achilles reflexes were present but diminished. A bilateral Babinski sign was present. Sense of motion and position of the toes was lost in both feet. Vibratory sensation was lost over the bony prominences of the lower extremities. Ataxia of both legs was present by the heel to knee test and was more

pronounced with the eyes closed. She walked with a slightly ataxic gait. The Romberg sign was positive. The chief disturbance in superficial sensibility was a diminution of pain and tactile sensation over the lower forearms and hands. The hemoglobin was 75 per cent and the red blood cells numbered 4,500,000.

COMMENT

This case illustrates several points. First, a considerable degree of functional recovery may occur in the absence of improvement of the neurologic signs. However, there is a possibility that postural sensibility partially returned as judged by the patient's descriptions, although the usual clinical tests failed to detect this. Second, while apparent improvement is taking place, evidence of increasing cord degeneration may occur, as shown by the appearance of a bilateral Babinski sign. Several observers have described cases of this type in which decrease of ataxia is accompanied by so-called improvement of the tendon reflexes. It is apparent that this phenomenon probably represents a progression of the spinal cord degeneration rather than a regression.

EFFECTS OF CESSATION OF LIVER TREATMENT

Six cases discontinued treatment for periods varying from four months to three years. In one, the signs and symptoms remained stationary over a period of three years without liver. In two, mild symptoms occurred during the relapse and improved under further treatment. In two others more severe neurologic manifestations followed the cessation of treatment and progressed in spite of a satisfactory regenerative response of the blood to further administration of liver. The sixth patient, in whom there were signs of posterior column involvement, showed progressive neurologic manifestations after a four month lapse of treatment notwithstanding the per-

sistence of high blood levels during this period (blood hemoglobin 105 per cent; red blood cells 5,400,000 per cubic millimeter).

Psychoses. Prominent psychotic manifestations were present in five patients. In two, there was a state of confusion; these patients responded well to treatment. The symptoms were more severe in three patients, who progressed in spite of fairly high blood levels and died three to five months after the onset of the psychoses.

DISCUSSION

Mention has been made previously of the conflicting opinions expressed by various authors concerning the effects of liver on the neurologic manifestations of pernicious anemia. This diversity, it was noted, may be partly explained by a difference in the criteria employed in determining the efficacy of treatment. Confusion still exists, however, when objective phenomena alone are considered. Curschmann⁶ has expressed himself definitely as denying any beneficial influence whatever of liver upon the spinal cord changes of the disease. He makes the statement "I have as yet not seen a single case of pernicious anemia in which the spinal symptoms, especially the sensory, motor and reflex disturbances, have been improved by liver treatment". In contrast are Ungley and Suzman⁷, who claim that, provided the treatment be adequate, considerable improvement in the neurologic lesion may be confidently expected. They found that vibration and joint sense returned in a number of their cases and that a Babinski sign disappeared in five out of nine cases. They con-

cluded that "all signs and symptoms of cord involvement may disappear."

A number of other authors have taken intermediate positions. Smithburn and Zerfas⁸, in a report based on a study of 115 cases of pernicious anemia, concluded that "improvement may occur in the neural and psychic changes" but also that "changes may develop for the first time or may steadily progress" during adequate treatment with liver extract. Needles⁹ has recently reported a series of 25 cases of pernicious anemia complicated by subacute combined degeneration, 11 of whom received adequate liver treatment. Signs of subacute combined degeneration appeared in five despite therapy, in four they remained stationary, while in two there was some evidence of improvement. In the two cases in which improvement occurred it concerned symptoms rather than signs.

In our series of 40 patients of pernicious anemia who received uninterrupted treatment with liver for an average period of 25 months, 27 patients presented signs of cord degeneration. Of these the treatment was adequate in 17 and in 10 the treatment was insufficient to maintain the proper blood levels. Of the well treated group subjective improvement, excluding the effect on paresthesias, occurred in six cases while evidence of favorable improvement on the neural process occurred in but one. As has been noted, in this case the improvement consisted of a return of joint sense in the lower extremities without return of vibration sensibility or change in the reflexes. In 10 of the 17 patients who received adequate

treatment there was objective evidence of progression of the cord degeneration, while in six the signs remained stationary. Of the patients who at their first examination presented no evidence of cord involvement, further observation showed that only one of nine well treated cases, and five of 10 poorly treated ones developed signs of cord degeneration.

While the number of patients studied in this group does not justify definite conclusions, certain deductions may be entertained. In the majority of cases of this series the spinal cord degeneration associated with pernicious anemia has progressed in spite of liver therapy. The rapidity of progression was variable. In some patients the degenerative process seemed to progress relentlessly; while in others, perhaps the majority, the progress of the neural changes was retarded. That improvement in cord changes is unusual is not surprising when one considers the character of the lesion and the inability of axis cylinders once destroyed to regenerate. Davison¹⁰, in an interesting histopathologic study of the cords of 17 cases of pernicious anemia with subacute combined degeneration, found progressive glial changes in the seven cases which were treated with liver. The untreated cases observed prior to the institution of liver treatment failed to show this glial reaction. The myelin sheaths and the axis cylinders in treated cases were not different from those in the untreated ones. He assumed that liver therapy caused a reduction in the amount or in the strength of the hypothetical toxin and therefore allowed the glia to proliferate and replace the damaged tissue.

It has not been definitely decided whether the axis cylinder or the myelin sheath is primarily affected in combined degeneration of the cord associated with pernicious anemia. While both structures are eventually destroyed, some investigators believe that the myelin sheath is affected first. If this is correct, institution of treatment may lead to functional restoration of the partly damaged nerve fiber. In this connection we may refer to Case II. This patient noted that the sense of position of her extremities improved to a certain degree several weeks after she began liver treatment. It is difficult to ascribe this partial return of position sense to any other factor but liver treatment.

CONSTITUTIONAL FACTORS

It is recognized that there is a definite tendency for pernicious anemia to occur in several members of a family. It is also a common observation that the disease occurs more frequently in individuals of a certain constitutional type. Among the characteristics of this type are fair complexion and premature graying of the hair. That there may be a familial tendency to the development of severe nervous manifestations is suggested by the patient presented as Case I and his brother who is mentioned there. In both, the initial symptoms and the clinical courses were similar. Symptoms began at relatively high blood levels and the cord degeneration progressed in spite of continuous treatment.

TREATMENT

Several factors must be considered in the treatment of pernicious anemia

accompanied by nervous manifestations. To be effective it should be given before degenerative changes in the cord are well established. We feel that treatment begun at this time is of value in the majority of patients, in the prevention of serious cord lesions. Certain patients, however, fail to respond in a favorable manner; in these the cord degeneration progresses in spite of persistent treatment.

Continued treatment appears advisable, as its interruption in several cases has been followed by aggravation of signs and symptoms referable to the nervous system. In one case, after liver was discontinued for a period of four months, the patient returned with more pronounced neurologic symptoms and signs although her red blood cell count was 5,400,000 and her blood hemoglobin 105 per cent.

The opinion has been expressed that whole liver is more effective in the treatment of subacute combined degeneration than liver extract. As all the patients in our series received both forms of treatment, we are unable to draw conclusions regarding their relative merits. The use of concentrated vitamin preparations has furnished no definite evidence of their value.

CONCLUSIONS

The use of liver is the most important measure in the treatment of pernicious anemia in all of its manifestations. Favorable effects have been noted in the amelioration of neurologic symptoms and possibly in a prevention or retardation of the spinal cord degeneration. In our opinion improvement in neurologic signs is unusual.

BIBLIOGRAPHY

- ¹MINOT, G. R., and MURPHY, W. P.: Treatment of pernicious anemia by a special diet, *Jr. Am. Med. Assoc.*, 1926, lxxxvii, 470-476.
- ²CONNER, H. M.: Improvement of neurologic manifestations of pernicious anemia; report of case, *Proc. Staff Meet., Mayo Clinic*, 1928, iii, 454.
- ³GILDEA, E. F., KATTWINKEL, E. E., and CASTLE, W. B.: Experimental combined system disease, *New Eng. Jr. Med.*, 1930, ccii, 523-527.
- ⁴MELLANBY, E.: The experimental production and prevention of degeneration in the spinal cord, *Brain*, 1931, liv, 247-290.
- ⁵HALL, G. W., and HIRSCH, E. F.: Paraplegia in flexion, with subacute combined degeneration of cord, *Arch. Neur. and Psychiat.*, 1930, xxiii, 257-265.
- ⁶CURSCHMANN, H.: Die Nervenstörungen der Biermerschen Anämie und die Lebertherapie, *Deutsch. Ztschr. f. Nervenhe.*, 1929, cxi, 151-159.
- ⁷UNGLEY, C. C., and SUZMAN, M. M.: Subacute combined degeneration of the cord: symptomatology and effects of liver therapy, *Brain*, 1929, lii, 271-294.
- ⁸SMITHBURN, K. C., and ZERFAS, L. G.: The neural symptoms and signs in pernicious anemia: the effects of liver extract, *Arch. Neur. and Psychiat.*, 1931, xxv, 1100-1110.
- ⁹NEEDLES, W.: Neurologic complications of pernicious anemia; effects of treatment with liver; a preliminary report, *Arch. Neur. and Psychiat.*, 1931, xxvi, 346-358.
- ¹⁰DAVISON, C.: Subacute combined degeneration of the cord: changes following liver therapy; a histopathologic study, *Arch. Neur. and Psychiat.*, 1931, xxvi, 1195-1219.

Cinchophen Hypersensitiveness*†

A Report of Four Cases and a Review

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INTRODUCTION

ALTHOUGH cinchophen and its compounds have been used in medicine for about twenty-four years, only recently have possible dangers from this drug been at all well known to the profession. While scattered reports of comparatively mild toxic side-actions are found in the literature from 1913 on, Worster-Drought's¹ case (published in 1923) of toxic hepatitis due to atophan was the first to call attention to this most serious complication of cinchophen therapy. Three years later, Evans,² Glover,³ and Willcox⁴ added additional cases to the British literature. In this country, Miss F. M. Painter, Assistant Editor of the Case Records of the Massachusetts General Hospital, observed from 1922 on several fatal cases of liver atrophy apparently following the use of weldona (a proprietary antirheumatic containing cinchophen). This observation was referred to by Cabot,⁵ who did not recognize cinchophen as the offending agent in the

preparation. In the last five years, reports of cases of liver damage in patients who had taken cinchophen have increased in an alarming fashion. Rabinowitz⁶ in 1930 was able to collect 50 such cases, with 25 deaths and 20 autopsies. It is probable, of course, that many of these cases are not reported and that many more patients with liver atrophy of apparently unknown etiology would, on careful questioning, have revealed the previous use of the drug. In view of these facts, the therapeutic use of cinchophen may well be again evaluated, as the number of reported cases would seem to preclude mere coincidence.

The lesion produced in the liver is not distinctive. It resembles very closely acute yellow atrophy due to other agents or of unknown etiology, or, when destruction is not so complete, the subacute yellow atrophy or toxic cirrhosis of Mallory.⁷ The wide variation in the dosage of the drug necessary to produce liver damage would seem to indicate that certain individuals have an idiosyncrasy or hypersusceptibility, while others enjoy a relative immunity and are able to take large doses over a long period with impunity.

It is proposed in this paper to review, not the more serious cases of

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liver damage due to cinchophen, but cases, principally of skin manifestations, which seem to demonstrate a true allergic reaction to the drug. It is believed that a review and analysis of these relatively minor complications may aid in the elucidation of the hepatic reactions. Four cases personally observed are also presented, one of them demonstrating a marked hypersusceptibility to cinchophen and to its compounds in a hypersensitive individual who also gave altered responses to a variety of other agents.

PHARMACOLOGY

Cinchophen, or phenyl-quinoline-carboxylic acid, was first used therapeutically under the name of atophan by Nicolaier and Dohrn⁸ in 1908. Several compounds of this drug have also been introduced, the most commonly employed being neocinchophen (tolsin, novatophan) or the ethyl ester of methyl cinchophen. The combination of iodine with cinchophen has been held, without clear evidence, to be especially efficacious in the treatment of rheumatic diseases, resulting in the sale of two proprietary remedies: oxyl-iodid, said to be the hydro-iodid of cinchophen, and farastan, or mono-iodo-cinchophen. Atophanyl, diiodoatophan, biloptin, quinophan, agotan, phenoquam, leucotropin, fantan, iriphan and weldona are listed by Rabinowitz⁹ as congeners of cinchophen. In addition it is probable that cinchophen or its derivatives make up a part of a large number of popular remedies for arthritis, thus adding a dangerous unknown quantity to the widespread use of the drug.

The actions of cinchophen and neo-

cinchophen resemble very closely those of the salicylates. Hanzlik⁹ has summarized the literature in a review published in 1926. Briefly, the actions include:

1. An increase in uric acid excretion through direct action on kidney permeability;
2. An antipyretic effect, not gained through depression of the metabolism, but through sweating and peripheral vasodilatation;
3. Analgesia, of unknown cause;
4. Depression of the leukocytes in rheumatic fever.

There is no definite evidence of a choloretic or antichemotic action, and any antiphlogistic effect is doubtful, unless perhaps through alteration in permeability of the capillaries or articular tissue or both, which might facilitate absorption. There are no data as to whether, as in the case of the salicylates, these drugs exert a depressant action on the streptococcus immune bodies; but Derick et al¹⁰ have shown that neocinchophen will nearly completely inhibit the formation of circulating antibodies in serum sickness due to horse serum. Cinchophen and neocinchophen are equally effective with the salicylates in relieving the symptoms of rheumatic fever. They are likewise not to be regarded in any way as specific in this disease, but represent a fortunate combination of analgesia and antipyresis. The analgesic action of the cinchophen compounds has been extended to other diseases causing long-continued pain, notably chronic arthritis, again without evidence of any specific effect on its course and with such improvement as occurs prob-

ably attributable to more normal use of the joints.

Both cinchophen and neocinchophen are but slightly soluble in water. The acidity of the former produces some irritation in the throat and stomach. It is probable that absorption of these drugs is nearly complete in the intestinal tract. The exact mode of excretion is not known, but the prevailing evidence goes to show that they are largely destroyed in the body with only slightly changed oxidation products being discovered in small amounts in the urine. Recently Lichtman¹¹ has found that in normal subjects, following the ingestion of 0.1 to 0.9 grams of cinchophen, amounts up to 21 per cent of oxy-cinchophen, 2 (ortho-hydroxy)-phenyl-quinoline-4-carboxylic acid, appear in the urine in the course of twenty-four hours. Excretion of this substance begins in two to three hours and is usually complete in twenty-four. He believes that oxy-cinchophen represents an intermediary product in the destruction of cinchophen by the liver. He has devised a simple colorimetric method for its quantitative determination in the urine. The results may be interpreted as a test for liver function, an increased excretion showing an interference in the catabolism of cinchophen beyond the stage of oxy-cinchophen due to diseased liver cells. In view of what is known concerning the effects of cinchophen upon the liver, we would be reluctant to advocate the use of this test, although the author has as yet observed no deleterious action in cases of hepatic disease.

The usual dosage of cinchophen and its compounds is from 22.5 to 45.0

grains (1.5 to 3.0 grams) daily. It has been found that from 10.0 to 13.0 grams of cinchophen and 11.0 to 16.0 grams of neocinchophen are necessary for complete effect, similar to salicylization in rheumatic fever. By this is understood the production of the so-called "toxic effect", with manifestations similar to those of salicylism.

As mentioned above, however, besides these therapeutic effects, there are side-actions of cinchophen and its derivatives which are often of grave danger to the patient. As yet, there has been no adequate pharmacological explanation of them. Splitting of the quinolin nucleus to liberate the benzene ring has been suggested by Ross¹² and others, but argued against by Sutton,¹³ Sherwood¹⁴ and Sollmann,¹⁵ since most of the benzene derivatives and the phenols do not injure the liver in overdoses. Furthermore, liver damage is as marked following the administration of aliphatic compounds, such as chloroform and carbon tetrachloride, and of phosphorus. The nitrobenzene compounds which might be produced by the oxidation of the quinolin nucleus are believed by Sutton¹³ and Sherwood¹⁴ to be responsible, in cases showing liver damage. Nitrophenols and nitrobenzenes all produce hepatic injury in certain cases. The failure of the kidney to excrete these substances and the existence of previous liver damage are postulated as adjuvant factors. So far, only theorizing is possible since objective evidence from experimentation is lacking, although a start has been made recently by Churchill and Van Wagoner.¹⁶ These authors have given massive doses of

cinchophen to dogs, with death resulting in three weeks. Autopsies showed varying degrees of liver necrosis, and impaired liver function was demonstrated during life by the bromsulfalein test and by diminution in urea formation. Two other dogs, with kidney damage created by a method of clamping the renal artery, have been given a dosage corresponding to the one used therapeutically in man. These animals have shown similar impairment in liver function, but were alive at the time of publication. These results may well represent a cumulative toxic action. Reichle,¹⁷ using rats, found that parenteral and enteral administration of cinchophen did not cause histologic changes characteristic of cinchophen poisoning in man. The livers of some of the animals were first depleted of glycogen by starvation, or were injured by carbon tetrachloride.

EXTRA-HEPATIC REACTIONS

A few cases have been reported showing toxic signs and symptoms which do not follow directly upon liver damage nor can be justly included in the group due to idiosyncrasy or allergic reactions, which we shall describe below. Kidney damage following full therapeutic or "toxic" dosage of cinchophen, demonstrated by the appearance of albumin, casts and white cells in the urine and diminished phthalein output, has been reported by Hanzlik.¹⁸ A similar action on the kidneys by the salicylates has been described. Schroeder¹⁹ mentions two cases of albuminuria following atophan administration. A tubular type of renal degeneration accompanying acute yellow atrophy has been noted at autopsy by several

observers (Evans,² Reichle,²⁰ Rake,²¹ Loewenthal,²² Sutton¹³). Beaver and Robertson,²³ in a recent review of the postmortem changes in fatal cinchophen hepatitis, expressed the belief that the pathologic changes were primarily in the liver and that "fatty changes in the heart and kidneys, mild fat necrosis of the pancreas, mucosal and serosal hemorrhages were . . . secondary to the toxic disturbances concomitant with atrophy of the liver". One case of acute pancreatitis has been reported by Petty²⁴ in a patient who took a "whole tubeful" of atophan for neuralgia. Laparotomy confirmed the diagnosis of pancreatitis; the liver appeared normal; the patient recovered. Coincidence, of course, cannot be excluded in this single case. Cases showing nausea, vomiting, and diarrhea without obvious liver damage or allergic manifestations may be accounted for by local irritation of the gastrointestinal tract.

ALLERGIC MANIFESTATIONS

Four cases personally observed showing typical symptoms of drug allergy are presented below. They are also included in the table which summarizes all the similar cases discovered in the literature.

CASE I

(No. 38 in the table) *Chronic arthritis; urticaria and bronchitis following the use of cinchophen.*

B. R., a Polish housewife, aged 35, was admitted to the medical service of the Massachusetts General Hospital on September 4, 1931, complaining of arthritis of ten months' duration, associated with severe sore throats for which a tonsillectomy had been performed two months before. No history of allergic disease in the patient or in her family was obtained, except for asthma in

an uncle. Examination disclosed only moderate joint changes characteristic of atrophic (rheumatoid) arthritis. The urine and blood were essentially normal. There was no eosinophilia.

Treatment was begun on September 9 with cinchophen 22.5 grains (1.5 grams) daily. Generalized urticaria developed nine days later on September 18, and the drug was discontinued the following day, after a total dosage of 225 grains (15 grams). The urticaria, along with a blotchy, itching erythema, gradually subsided in the course of the next week. During this period, her arthritis seemed definitely improved, but she was bothered by a non-productive cough, which lasted for about three weeks. There were no abnormal physical signs in the lungs, and a roentgenogram of the chest taken on October 6 was negative. On September 21, two days after discontinuing the cinchophen, the icteric index and quantitative Van den Bergh tests were within normal limits. Further treatment was carried on by a series of nine intravenous injections of mixed typhoid-paratyphoid vaccine with improvement in her arthritis and no untoward effect except for the development of herpes labialis on October 4, following the third injection. From then on, the progress of the patient was uneventful. When seen on January 18, 1932, four months after her skin reaction to cinchophen, she was nearly free from arthritis, and intradermal tests with a 1/500 solution of cinchophen were negative.

COMMENT

In this case, there is no evidence of an acquired sensitivity, unless we consider that the ingestion of 15 grams over nine days before symptoms began was sufficient to produce it. It is quite possible that the patient had received the drug in the course of the treatment of her arthritis before coming to the hospital. The "bronchitis", which lasted about three weeks, corresponds to that observed in two of Schilling's²⁷ cases (Nos. 28 and 30 in the table) and may well be an allergic manifestation. In contrast to Case III (see below), mixed typhoid vaccine intravenously caused no urticarial response. No evidence of liver damage could be obtained by the usual tests.

CASE II

(No. 39 in the table) Gout; urticaria and epigastric distress following the use of farastan (mono-iodo-cinchophen).

M. I., an Italian fisherman, aged 54, was admitted to the medical service of the Massachusetts General Hospital on December 3, 1931, complaining of inflammation of the right wrist of five weeks' duration. During the past two years he had had two attacks of pain, swelling and redness of the great toes of each foot, with complete freedom from symptoms between the attacks. Ten days before admission, a physician had given him farastan (mono-iodo-cinchophen), 22.5 grains (1.5 grams) daily for four days, a total dosage of 90 grains (6 grams). The use of the drug was then discontinued on account of epigastric distress, and three days later generalized urticaria had appeared, which had continued until admission.

The past history included gonorrhea twenty-four years before, and malaria in 1914. There was no family history of gout and none of allergic disease in patient or family.

Examination showed itching, erythematous areas over thighs, arms, palms and soles, with several wheals. Swelling, tenderness, and pain on motion were present in the right wrist.

The urine and blood were negative, with no eosinophilia. The non-protein-nitrogen was 29 milligrams and the uric acid 5.2 milligrams per 100 cubic centimeters of blood. No pus could be expressed from the prostate. Roentgen examination showed abscessed teeth, but no changes characteristic of gout in the hands or feet.

After admission, the rash lasted three days, accompanied by epigastric distress and pain on swallowing. December 5, eight days after omission of the drug, the liver function (Rosenthal), the icteric index and the quantitative Van den Bergh tests were all normal. Carbohydrates were forced in the patient's diet, to guard against possible liver damage from cinchophen. While on the ward, his right wrist improved, but he developed a dusky, tender swelling of the right second metatarso-phalangeal joint. A diagnosis of gout was made, a low purine diet instituted and the abscessed teeth re-

moved. By discharge on December 23, the arthritis had greatly improved.

The patient was seen in the out-patient department on January 30, 1932, about two months after his skin reaction, and was found to be nearly symptom-free. Intradermal tests with a 1/500 solution of cinchophen were negative.

COMMENT

This case is quite similar to Case I in the absence of direct proof of acquired sensitivity (although it is quite probable that he had received similar treatment in his previous attacks), in negative tests for disturbance in liver function and in negative skin reactions.

CASE III

(No. 40 in the table) *Chronic arthritis; cinchophen used once without reaction, but six months later, its administration followed by urticaria and fever, with a similar response to repeated small doses; patient hypersensitive to a variety of other agents.*

H. D., a white, married, native cook, aged 57, was admitted to the medical service of the Massachusetts General Hospital on October 11, 1930, complaining of arthritis of one year's duration. Her past history included chronic constipation, frequent sore throats, and double oophorectomy and appendectomy fifteen years before. There was no family history of allergic disease, except for occasional attacks of urticaria in a sister, but the patient herself had had one attack of urticaria ten years before, mild and of brief duration, without known cause.

At the onset of her illness, one year before admission, she had taken a proprietary drug (eucophen) up to a total dosage of about 30 grains (2.0 grams) of cinchophen, without toxic symptoms. Six months before admission, she took during a single week about 69 grains (4.6 grams) of oxyliodid, a proprietary compound said to be the hydro-iodid of phenylcinchoninic acid, containing 33 per cent iodine and 67 per cent cinchophen. The next day, shortly after taking one capsule containing 3 grains (0.2 gram), she was seized with chills, fever, generalized aching and severe urticaria, lasting thirty-six hours. From then on, although omitting the drug, she continued

to have intermittent, frequent attacks of urticaria, without relationship to exacerbations of her arthritis, which became worse.

Examination on admission showed weight loss, arteriosclerosis of retinal and peripheral vessels, enlargement of the heart to the left with accentuation of the aortic second sound and a blood pressure of 175 millimeters of mercury systolic and 100 diastolic. Moderately severe atrophic (rheumatoid) arthritis involved especially the hands, wrists and knees.

Laboratory tests revealed normal findings in the blood (including absence of eosinophilia), pyuria, a negative Hinton test, and normal values for blood non-protein-nitrogen, blood uric acid, icteric index, gastric acidity and basal metabolism. A quantitative Van den Bergh test was normal. Roentgenogram disclosed changes in the joints consistent with atrophic arthritis; a low position of the colon; and essentially negative teeth, sinuses and gall-bladder. Intradermal and scratch tests with the common food and dust allergens were negative.

Treatment was started with a high vitamin diet, salicylates, measures against constipation and renal lavage for pyelitis. A sample of "proteose", isolated from the urine during an attack of urticaria according to the method of Oriel and Barber⁴² gave positive local and focal reactions. In the course of the next two months, desensitization was attempted with small doses of this "proteose". During this treatment, the patient's urticaria lessened and her arthritis improved, but not without one or two severe urticarial attacks apparently due to overdosage with the "proteose".

January 14, 1931, she was given 7.5 grains (0.5 gram) of farastan (mono-iodo-phenylcinchophen). At this time, we were unaware that her previous urticaria had been caused by cinchophen. Four hours later she had a shaking chill, arthralgia, and cyanosis of the extremities, followed by fever, which had risen to 104° F. Ten hours after administration of this drug, the white blood count was 5,800 and the urine examination negative. In the course of the next hours, her temperature returned to normal, but severe generalized urticaria appeared, gradually subsiding in forty-eight hours. No

other cause for her fever and urticaria was found. Her joints seemed definitely improved following this reaction.

January 19, five days later, she was again given 7.5 grains (0.5 gram) of farastan with an exactly similar reaction, including chills, fever to 102° F. and urticaria, of like duration. The joints again seemed to be improved. In order to test the patient's sensitivity to iodine, Lugol's solution, 10 minims thrice daily was administered for a day without reaction. In the course of the next two weeks, she was given two intravenous injections of mixed typhoid-paratyphoid vaccine (15 and 20 million organisms respectively). A rise in temperature of about two degrees was secured with each injection followed by urticaria of about forty-eight hours' duration. The joints showed marked improvement after these reactions.

March 16, two months after her reaction to this drug, scratch tests with farastan in powder form and dissolved in N/10 sodium hydroxide were negative. Ten days later, the patient was given 7.5 grains (0.5 gram) of cinchophen with an ensuing reaction almost exactly similar in character and duration to that obtained after farastan, with a temperature rise to 104° F., urticaria lasting forty-eight hours and improvement in her arthritis. (Figure 1) Three days after the administration of cinchophen, Van den Bergh's test was negative for bilirubinemia.

April 9, a liver function test was done

by Rosenthal's method, resulting in no retention of the dye in thirty minutes. This test was followed by a reaction milder, though similar to those obtained with cinchophen, starting about three hours after the administration of the bromsulfalein. Three days later, scratch tests with cinchophen in dilutions of 1/50 and 1/500 and bromsulfalein in dilutions of 1/20 and 1/200 were negative. Just before her discharge on April 14, attempted transfer of the patient's sensitivity to the skin of two normal subjects by intradermal injection of her serum (Prausnitz-Küstner reaction) was unsuccessful, using cinchophen in a dilution of 1/500. During her hospital stay, she received methyl salicylate (externally), sodium salicylate, luminal, aspirin, Lugol's solution and amidopyrin without untoward effect.

The patient's course was then followed in the out-patient department. April 25, one month after her last reaction to cinchophen, intradermal tests with a 1/500 solution of cinchophen were negative. About June 1, she had an attack of urticaria lasting twenty-four hours accompanied by a gastric upset but without chill or fever. Its cause was unknown. About July 20, she sunburned her legs severely, with a resulting inflammatory edema lasting a week. This was also followed by urticaria lasting two days, and by marked improvement in her arthritis.

October 18, 1931, the patient was brought into the hospital again for a treatment with general diathermy. This consisted in ele-

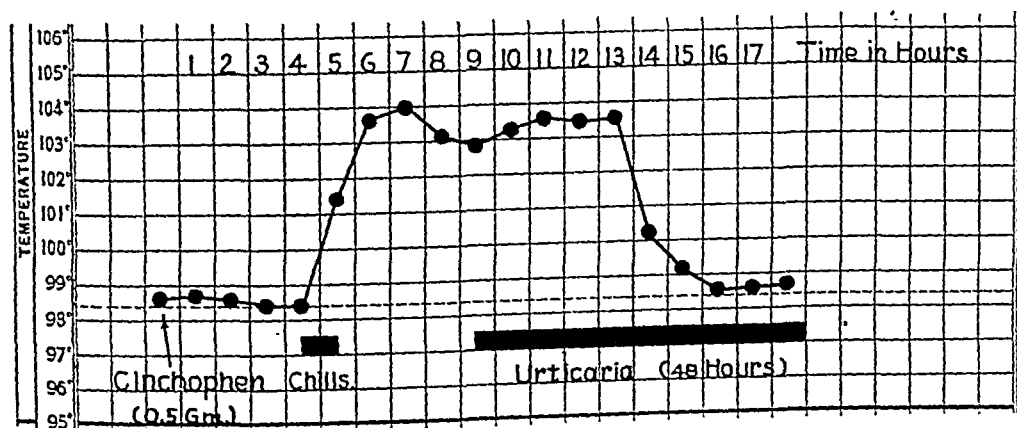


FIG. 1. Temperature chart of Case III, following the ingestion of 0.5 gram of cinchophen.

vating her temperature to about 104° for four hours, by means of the passage of a high frequency alternating current through her body, with insulation to prevent the loss of heat. The method has been described by Neymann⁴³ and others. Urticaria began about four hours after the patient's temperature had reached 104° and continued for about thirty-six hours. Improvement in the joints was not so marked as following previous febrile attacks.

January 8, 1932, ten months after her last attack of urticaria due to cinchophen, intradermal tests with a 1/500 dilution of cinchophen were again negative.

COMMENT

This patient well illustrates an acquired sensitivity to cinchophen, since her urticaria first appeared following her second course of treatment with this drug. She seems to have developed an increasing sensitiveness; she did not react at all to the first course of two grams, she reacted in the second course only after the administration of 4.8 grams, and thereafter she showed an immediate, accelerated reaction within five hours after the ingestion of 0.5 gram. The duration (eight months) of her urticaria, which evidently began as an allergic drug reaction, is unusual. Perhaps she became sensitive to new extrinsic or to intrinsic (bacterial) allergens. Her febrile manifestations were not unusual. Coca⁴⁴ mentions fever as one of the most frequent symptoms of drug allergy, with temperatures of 104-106° F. frequently recorded. In Menninger's⁴⁵ cases of skin eruptions due to phenobarbital, 51 per cent showed febrile responses. Twenty-five per cent of the cases included in the table experienced a rise in temperature.

It is of interest that this patient showed multiple sensitivity, with identical reactions, to oxyl-iodid, farastan, atophan and brom-sulfalein. The common factor in the first three must of course be the cinchophen group. The last is not closely related chemically to the others, but it also is taken up and disposed of by the hepatic cells. In a survey of the larger series of cases^{46, 47, 48, 49} in the American literature in which the Rosenthal test was used, a total of 473

patients, no reports of general reactions were found. The urticarial response is probably, then, one dependent upon an unusually hypersensitive individual. We do not consider the urticaria following fever from typhoid vaccine, sunburn, and general diathermy to represent a true allergic reaction, but believe that it may well follow the release of histamine-like substances from damaged cells.

CASE IV

"Neuralgia"; urticaria and liver damage, following the use of atophan; death from sepsis; autopsy.

C. G., an American housewife, aged 60, was admitted to the medical service of the Massachusetts General Hospital on December 28, 1931, complaining of vomiting and chilliness for twelve hours.

The past history included dyspnea on exertion, chronic cough, occasional edema of the ankles and much "gas" for several years. She had suffered from "neuralgia" of the left arm for fifteen years.

About four weeks before admission, she burned her left shoulder with an electric pad. Atophan was incidentally prescribed for relief of her neuralgic pain and in the course of the next two weeks she received about 200 grains (13 grams) of this drug. At the end of this time the use of the drug was discontinued following the appearance of generalized urticaria which persisted for a week. The burn had diminished in size but was not completely healed. For twelve hours before admission, she had vomited continually, and had had chilly sensations.

Examination showed a granulating wound on the left shoulder, the heart slightly enlarged, a systolic murmur, no jaundice, and the liver edge not palpable, although liver dullness continued for about an inch below the costal margin.

Laboratory tests revealed a negative urine, red blood cell count of 3,700,000, hemoglobin 60 per cent (Tallquist), and white blood cell count 20,000 with 92 per cent polymorphonuclear cells and no eosinophils.

The temperature ranged from 102° to 103° F. and the pulse was 110.

During the next two days she continued to vomit. December 30, the quantitative Van den Bergh showed 3.7 milligrams bili-

rubin per 100 cubic centimeters of blood and a liver function test (Rosenthal) disclosed 38 per cent retention at the end of a half hour. A probable diagnosis of acute yellow atrophy of the liver due to cinchophen was made. During the next week, the patient was treated with intravenous glucose and seemed to improve. Her vomiting ceased but she continued to run a fever of 101° to 102° F. and pulse of 100. There was still no definite clinical jaundice and the liver was unchanged in size on physical examination.

January 8, 1932, phlebitis of the left antecubital vein developed and the next day an indurated, red, non-tender mass the size of an egg appeared in the left axilla. This was treated by poulticing. January 10, she suddenly became dyspneic, her pulse rate rose to 150, and signs of consolidation appeared at the left base. Her temperature mounted to 105° F. and the patient died the next day. Pulmonary infarction was believed to be the most likely cause of death. Autopsy revealed a large sub-pectoral abscess on the left, pneumonia, and signs of a generalized sepsis. Grossly, the liver showed no evidence of acute yellow atrophy. Microscopically, central necrosis was found, with a few other scattered areas of hepatic cell destruction. It was believed that the histologic picture in the liver was compatible with either sepsis or cinchophen poisoning.

COMMENT

In this patient, the first sign of idiosyncrasy to the drug was the development of urticaria following the administration of 13 grams of atophan over two weeks. We have no knowledge as to whether she had previously been exposed to cinchophen, but believe it quite likely in the course of a painful illness lasting fifteen years. Prompt omission of the drug did not prevent the development of liver damage, manifesting itself clinically about two weeks later. Although she showed unmistakable signs of hepatitis due to cinchophen early in the course of her illness, the sepsis which developed was responsible for her death, and the histologic findings in the liver were equivocal in nature. Perhaps her resistance to infection was lowered by the hepatic injury. This

would be in accordance with frequent clinical observations.

DISCUSSION

In the table are summarized 41 cases of allergic reactions to cinchophen and its compounds, including all the cases which were found in the literature and the four presented in this paper. We have used only cases in which full reports are given and have therefore omitted mere references to this condition. We have also omitted 25 cases of urticaria occurring in the course of the use of farastan and reported without details in a combined series^{50, 51} of 1389 cases, (an incidence of 1.7 per cent).

The average age of the tabulated cases was 49, a figure perhaps influenced by the fact that the cases treated were largely sufferers from chronic arthritis or gout. Twenty-five, or 61 per cent, were in females and 39 per cent in males. The amount of the drug used before symptoms appeared varied from one gram to 115 grams, the average being 16.6 grams. The duration of administration was two weeks or less in all but five instances, with 5.3 days as an average.

Thirty-five of the 41 cases used cinchophen or atophan before symptoms began, two neocinchophen and two farastan. One patient was found sensitive to both atophan and novatophan and one (No. 40) to oxyl-iodid, farastan and cinchophen. In common with other drugs which often cause allergic skin manifestations, cinchophen and its compounds seem to be more prone to cause one type of dermatitis, although not to the exclusion of several others. In this series, the urticarial type, with erythema, wheals

TABLE I

Case Number	Author and Bibliography	Age	Sex	Preparation Used	Amount and Duration of Usage	Type of Reaction or Allergic Dermatitis	Other Symptoms	Dosage before Second Attack	Interval Between Attacks	Nature of Second Attack	Remarks
1	De Oyarzabal ²¹	?	M	Neotophan	1.5 gms. (?) 12 hours	"Itching dermatitis, eczema-like."	None	Same	"Some months"	Same	
2	von Müller ²²	23	F	Atophan	6 gms. (?) "Several days"	Scarlatiniform, itching	Fever of 102°F.	Same	?	Same	Same experience repeated twice with same dosage, not with a smaller dose.
3	Phillips ²³	56	M	Atophan	20 gms. 10 days	Purpuric	None	8 gms.	7 days	Same	Repeated with soda bicarbonate; rash milder and lasted only 3-4 days.
4	Ibid ²³	45	M	Atophan	4 gms. 2 days	Urticaria	None	4 gms.	7 days	Same	
5	Ibid ²³	72	F	Atophan	1 gm. 6 hours	Urticaria	None	1 gm.	7 days	Same	
6	Ibid ²³	65	F	Atophan	45 gms. 1 month	Urticaria	None	2 gms.	7 days	Same	
7	Ibid ²³	53	F	Atophan	2 gms. 1 day	Scarlatiniform, itching	None	3 gms.	4 days	Fever 103°F., chill, no dermatitis	
8	Herrick ²³	38	F	Atophan	27 gms. 9 days	Scarlatiniform, generalized except face	Fever of 103°F., headache, vomiting, prostration	?	One month	Same	Atophan given a few months before without reaction.
9	Marañón ²³	?	M	Atophan	?	Erysipelas-like on head and neck	Chills, fever, depression, scanty urine with extraordinary proportions of uric acid	One tablet	"Few weeks"	Same	Atophan given a few months before without reaction.
10	Ibid ²³	?	?	Atophan	"One tablet"	Pruritus without eruption	Chills, fever, depression	1 gm.	One month	Papular erythema of face with edema	Generalized pruritus, vomiting, fever of 100°F., accompanied the second attack.
11	Huber-Pestalozzi ²⁰	56	F	Atophan	17 gms. 18 days	Urticarial and scarlatiniform, generalized except face	None	1.5 gms.	Several days	Red, scaling plaques on face and neck with edema and fever of 101°F.	Six weeks later, similar reaction to 1 gm. of atophan. Atophan used for several years before without reaction.
12	Brammer ²¹	38	F	Atophan	20 gms. 10 days	Pruritus generalized	None				
13	Kissmeyer ²²	70	M	Atophan	3 gms. 1 day	"Red spots" on face and neck, and edema	None				

14	Thomsen ¹³	30	F	Atophan	4.5 gms. 3 days	Scarlatiniform of face and neck	Slight malaise					
15	Schroeder ¹⁰	37	M	Atophan	20 gms. 10 days	Generalized itching exanthem with edema	Fever, Albuminuria					Chronic nephritis and death en- sued, ? relationship to atophan.
16	<i>Ibid</i> ¹⁰	46	M	Atophan	40 gms. 3 weeks	Multiform, itching, with wheals, edema, erythema, bullae	Albuminuria extra-systoles	1.5 gms.	6 months	Same, less severe		
17	<i>Ibid</i> ¹⁰	39	F	Atophan	?	Urticaria, edema	Palpitation, vomiting, rectal bleeding					
18	<i>Ibid</i> ¹⁰	50	F	Atophan	25.5 gms. 11 days	Generalized papular urticaria, edema	Fever of 101.5°F. bladder tenesmus, laryngeal obstruction					Tracheotomy nearly necessary.
19	<i>Ibid</i> ¹⁰	38	F	Atophan	28.5 gms. 11 days	Papular with edema and itching, becom- ing purpuric	Fever of 100.5°					
20	<i>Ibid</i> ¹⁰	53	F	Atophan	39 gms. 15 days	"Reddish, itching exanthem"	None					
21	<i>Ibid</i> ¹⁰	57	F	Atophan	21 gms. 14 days	Papular, itching, with infiltration	Headache					Dermatitis following veronal 4 years before.
22	<i>Ibid</i> ¹⁰	34	F	Atophan	8 gms. 2 days	"Itching exanthem"	None	8 gms.	?	Same		Retested twice with same dos- age and result.
23	<i>Ibid</i> ¹⁰	44	F	Atophan and novatophan	21 gms. 8 days	Multiform, with urticaria, edema, papules, erythema	Pyrosis	24 gms.	18 days	Same, less severe		Novatophan used preceding sec- ond reaction.
24	Worster- Drought ¹	59	M	Atophan	16 gms. 12 days	Urticaria	None	0.5 gm.	3 weeks	Same, more severe		Second attack followed by jaun- dice for 3 weeks with recovery.
25	Scully ²⁴	48	M	Cinchophen	"One dose"	Vasomotor collapse	Tachycardia, chill, apprehension, low blood pressure	"One dose"	?	Same		Similar reaction 6 months be- fore after single tablet.
26	Barron ³⁵	44	M	Cinchophen	"2 tablets"	Syncope and vaso- motor collapse	None	"2 tab- lets"	3 months	Same, with erythema and edema		Urine contained albumin. Skin tests negative.
27	Boots and Miller ³⁶	?	M	Neo- cinchophen	2 gms. in single dose	Urticaria	Slight trace of albumin and casts 2 hours later					Patient known to have idiosyn- crasy for salicylates.
28	Schilling ³⁷	74	F	Atophan	1.5 gms. One day	Erythema, edema, itching, "aphthous" ulcers in mouth	None	0.3 gm.	2 years	Same, with dry bron- chitis but no erythema		Bronchitis lasted for weeks.
29	<i>Ibid</i> ³⁷	73	F	Atophan	15 gms. for 10 days	"Aphthous" ulcers in mouth	None					

TABLE I—Continued

Case Number	Author and Bibliography	Age	Sex	Preparation Used	Amount and Duration of Usage	Type of Dermatitis or Allergic Reaction	Other Symptoms	Dosage before Second Attack	Interval between Attacks	Nature of Second Attack	Remarks
30	<i>Ibid</i> ²⁷	?	F	Atophan	0.5 gms. in single dose	Edema of eyelids and "aphthous" ulcer in mouth	Fever and dry bronchitis				Given 1.5 gms. daily for 5 weeks following.
31	<i>Ibid</i> ²⁸	39	F	Atophan	1 gm. in single dose	Scarlatiniform	Circulatory collapse				Eruption occurred during jaundice along with attacks of angioneurotic edema of head, arms and larynx.
32	Sutton ²⁹	27	F	Cinchophen	37 gms., ? duration	Generalized, itching, papular	Jaundice, vomiting, fever. Death from acute yellow atrophy				Past history of asthma with positive skin tests. Six months later, skin tests positive for cinchophen.
33	Fink ²⁸	47	M	Cinchophen	14 gms. 4 weeks	Urticaria, purpura	Jaundice with recovery				Past history of urticaria due to strawberries. Father asthmatic. Six months later, skin tests positive for cinchophen.
34	<i>Ibid</i> ²⁸	54	M	Cinchophen	27 gms. 9 days	Urticaria	Latent jaundice				Farastan taken for one or two days a year before and discontinued on account of epigastric discomfort. Intradermal tests negative 3 weeks later.
35	Miller ²⁰	54	F	Farastan	10.5 gms. 7 days	Urticaria, edema, erythema; later morbilliform and papulo-vesicular	Nausea, anorexia, vertigo, confusion				Treated with intravenous glucose and intraduodenal magnesium sulfate.
36	Eimer ⁴⁰	52	M	Atophan	115 gms. 41 days	Morbiliiform, purpuric	Severe jaundice with recovery				Drug contained in proprietary remedy for rheumatism.
37	Jr. Am. Med. Assoc. Bureau of Investigation ⁴¹	?	F	Cinchophen	One gm. or less in single dose	Bright red rash from waist up. Edema of tongue and throat	Circulatory collapse				Intradermal tests with 1/500 cinchophen negative 4 months later.
38	Authors' Cases	35	F	Cinchophen	15 gms. 10 days	Urticaria, erythema	Non-productive cough for 3 weeks				Intradermal tests with 1/500 cinchophen negative 2 months later.
39	<i>Ibid</i>	54	M	Farastan	6 gms. 4 days	Urticaria, erythema	Epigastric distress, pain on swallowing				Repeated twice with same result. Skin tests negative.
40	<i>Ibid</i>	57	F	Cinchophen oxy-iodid Farastan	4.6 gms. 1 week	Urticaria, edema	Chills, fever	0.5 gm. of farastan	9 months	Same	
41	<i>Ibid</i>	60	F	Atophan	13 gms. 2 weeks	Urticaria	None				Followed by fever, vomiting, jaundice and evidence of liver damage.

or subcutaneous edema, was most frequently found, occurring in 16 cases. A scarlatiniform eruption was noted in six and a papular in five. Other types described included purpuric, morbilliform, vesicular and bullous lesions. Three cases cited by Schilling³⁷ showed "aphthous" ulcers in the mouth. As mentioned before, fever accompanied the dermatitis in about 25 per cent of the cases. Five showed various gastrointestinal symptoms (exclusive of jaundice), and in three, albuminuria was noted. In four cases, alarming syncope with vasomotor collapse took place, all recovering. Three of these also had skin eruptions. Rectal bleeding and bladder tenesmus were two other possibly allergic manifestations noted.

In view of the present conception expressed by Rackemann,⁵² that, "little doubt remains but that hypersensitiveness in man is acquired, just as typical anaphylaxis in animals is acquired," it is interesting that 14, or about a third of the cases, developed symptoms after exposure over a period of two days or less, many apparently showing an allergic type of response after a single administration of the drug. In only two of this group was a definite history obtained of a previous use of cinchophen unaccompanied by manifestations of hypersensitiveness. However, with the multitude of proprietary mixtures containing cinchophen and the propensity of sufferers from the arthritic diseases to sample many different remedies, it seems quite likely that previous exposure may have actually taken place without the observer's knowledge.

The mechanism of the acquisition

of hypersensitivity from simple non-protein substances such as cinchophen is as yet not completely understood, although some insight into this problem is given by the work of Landsteiner,⁵³ who has been able to combine many of these substances with homologous animal sera, and thus create compound proteins which have immunologic activity comparable to foreign serum. It is possible to suppose that some such combination may be formed in vivo. The patient might thus become sensitized shortly after the first administration of the drug. The variable, individual response to this sensitization would control not only the appearance or non-appearance of symptoms on further administration, but also their extent and duration when they do appear. In every case in which cinchophen was re-administered, an allergic type of response was elicited, often after a single dose. This reaction was essentially the same in most instances as the initial one, although in one case the dermatitis was absent in the second attack (fever and chill being the only manifestations), while, in another, only the second attack of vasomotor collapse was accompanied by an erythematous eruption. This constancy of response to re-administration (in two cases the patient was retested three times) would be fully compatible with a specific, acquired sensitivity.

Skin tests to cinchophen were negative in six cases, and positive in only two (Fink³⁸), both of these giving a previous history of allergy. Three additional cases (Nos. 21, 27 and 40), also gave a story of hypersensitivity in the past, the first to veronal, the second to salicylates, while the last had

had urticaria of unknown etiology. According to Zinsser,⁵⁴ positive skin reactions in drug sensitivity are not often obtained and "passive local homologous sensitizations by the Prausnitz-Küstner reaction have in general been negative."

In six of the 41 cases, the allergic manifestations were associated with evidence of liver damage. Three of these (Nos. 24, 33 and 34) showed evidence of mild liver involvement immediately following an attack of urticaria, in one (No. 34) a positive Van den Bergh test being the only clue. Worster-Drought's¹ classical case (No. 24), had urticaria following the ingestion of 16 grams in twelve days; three weeks later the patient took only 0.5 gram, with resultant more severe urticaria and jaundice lasting three weeks before recovery. In two other patients (Nos. 32 and 36), the skin eruption accompanied the severe jaundice, along with attacks of angio-neurotic edema in one (No. 32). Although the number of cases is not large, it is easy to see that dermatitis due to cinchophen may be followed by liver damage. Furthermore, as evidenced by cases 33, 34, and 41, immediate cessation of the drug may not prevent this more serious complication. However, as opposed to Worster-Drought's¹ one case where the premonitory urticaria was disregarded and jaundice followed the second administration of the drug, there are 18 other cases which were retested with the drug and Schilling's³⁷ patient (No. 30) to whom cinchophen was given for five weeks

following the appearance of allergic manifestations—all without evidence of hepatic injury. In three of our cases, tests for liver function were normal during or shortly following the appearance of the rash. It is impossible, then, to state that dermatitis occurring in the course of cinchophen administration is necessarily an ominous sign and that liver damage will follow. But we do wish to reemphasize that its appearance should call for immediate and final withdrawal of the drug, along with measures designed to protect the liver, such as the forcing of carbohydrate.

SUMMARY AND CONCLUSIONS

1. Four cases of allergic reactions to cinchophen and its derivatives are presented in detail, and 37 others are summarized from the literature.

2. The pharmacology and the therapeutic and toxic actions of this group of drugs are briefly reviewed.

3. Many cases appear to show an idiopathic, non-acquired sensitiveness, but previous use of the drug is not entirely ruled out.

4. Re-administration has invariably produced a similar allergic reaction, often following immediately upon the first dose.

5. While only six cases were associated with hepatic involvement, the appearance of dermatitis or other allergic manifestations is believed to indicate: first, the immediate and final withdrawal of the drug; second, the prophylactic administration of glucose for at least one week.

BIBLIOGRAPHY

- ¹WORSTER-DROUGHT, C.: Atophan poisoning, *Brit. Med. Jr.*, 1923, i, 148-149.
- ²EVANS, G.: Atophan derivatives in rheumatism, *Brit. Med. Jr.*, 1926, ii, 93.
- ³GLOVER, L. G.: Atophan derivatives in rheumatism, *Brit. Med. Jr.*, 1926, ii, 136.
- ⁴WILLCOX, W. H.: Atophan derivatives in rheumatism, *Brit. Med. Jr.*, 1926, ii, 273-274.
- ⁵CABOT, R. C.: Case records of the Massachusetts General Hospital, Boston Med. and Surg. Jr., 1925, xccii, 1122-1126.
- ⁶RABINOWITZ, M. A.: Atrophy of liver due to cinchophen preparations, *Jr. Am. Med. Assoc.*, 1930, xcv, 1228-1233.
- ⁷MALLORY, F. B.: Cirrhosis of the liver; five different types of lesion from which it may arise, *Johns Hopkins Hosp. Bull.*, 1911, xxii, 69-75.
- ⁸NICOLAIER, A., and DOHRN, M.: Über die Wirkung von Chinolincarbonsäure und ihrer Derivate auf die Ausscheidung der Harnsäure, *Deutsch. Arch. f. klin. Med.*, 1908, xciii, 331-335.
- ⁹HANZLIK, P. J.: Actions and uses of the salicylates and cinchophen in medicine, *Medicine*, 1926, v, 197-373.
- ¹⁰DERICK, C. L., HITCHCOCK, C. H., and SWIFT, H. F.: Effect of anti-rheumatic drugs on the arthritis and immune body production in serum disease, *Jr. Clin. Invest.*, 1928, v, 427-440.
- ¹¹LICHTMAN, S. S.: Cinchophen oxidation test of function of hepatic cells, *Arch. Int. Med.*, 1931, xlviii, 98-125.
- ¹²ROSS, J. B.: Liver damage following cinchophen preparations, with report of 5 cases, *Canad. Med. Assoc. Jr.*, 1931, xxiv, 632-634.
- ¹³SUTTON, D. C.: Acute yellow atrophy of liver following taking of cinchophen; report of case, *Jr. Am. Med. Assoc.*, 1928, xci, 310-312.
- ¹⁴SHERWOOD, K. K., and SHERWOOD, H. H.: Acute toxic hepatitis (acute yellow atrophy) due to cinchophen; report of case, *Arch. Int. Med.*, 1931, xlviii, 82-88.
- ¹⁵SOLLMANN, T.: In discussion of Rabinowitz,⁶
- ¹⁶CHURCHILL, T. P., and VAN WAGONER, F. H.: Cinchophen poisoning, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 581-582.
- ¹⁷REICHLE, H. S.: Cinchophen poisoning; attempt to produce toxic cirrhosis of liver in rats, *Arch. Int. Med.*, 1932, xlix, 215-220.
- ¹⁸HANZLIK, P. J., and SCOTT, R. W., et al: Cinchophen, neocinchophen, and nov-aspirin in rheumatic fever; comparative therapeutic efficiency, toxicity and renal functional effects, *Jr. Am. Med. Assoc.*, 1921, lxxvi, 1728-1734.
- ¹⁹SCHROEDER, K.: Atophan poisoning, *Ugesk. f. Laeger, Kobenh.*, 1922, lxxxiv, 1141-1153.
- ²⁰REICHLE, H. S.: Toxic cirrhosis of liver due to cinchophen, *Arch. Int. Med.*, 1929, xlii, 281-288.
- ²¹RAKE, G. W.: Case of subacute yellow atrophy following taking of atophan, *Guy's Hosp. Rep.*, 1927, lxxvii, 229-237.
- ²²LOEWENTHAL, L. J. A., MACKAY, W. A., and LOWE, E. C.: Two cases of acute yellow atrophy of the liver following administration of atophan, *Brit. Med. Jr.*, 1928, i, 592-593.
- ²³BEAVER, D. C., and ROBERTSON, H. E.: Specific character of toxic cirrhosis as observed in cinchophen poisoning; review of 5 fatal cases, *Am. Jr. Path.*, 1931, vii, 237-258.
- ²⁴PETTY, M. J.: Acute pancreatitis following ingestion of excessive amount of atophan, *Brit. Med. Jr.*, 1928, ii, 442.
- ²⁵DE OYARZABAL, E.: Dermatitis artificial, tipo eczema, producida por el atofan, *Rev. espan. de dermat. y sif.*, 1913, xv, 301-303.
- ²⁶VON MÜLLER, A.: Nebenwirkung des Atophans, *Gesellsch. f. innere Med. u. Kinderheil. in Wien*, Feb. 13, 1913; abstr., *Therapeut. Monatschr. Berlin*, 1913, xxvii, 468.
- ²⁷PHILLIPS, J.: Skin rashes following the administration of atophan, *Jr. Am. Med. Assoc.*, 1913, lxi, 1040.
- ²⁸HERRICK, W. W.: A scarlatiniform rash from atophan, *Jr. Am. Med. Assoc.*, 1913, lxi, 1376-1377.
- ²⁹MARAÑON, G.: *Revista Clinica de Madrid*,

- July 30, 1914; abstr., *Acute toxic reaction to atophan*, Jr. Am. Med. Assoc., 1914, lxiii, 2254.
- ³⁰HUBER-PESTALOZZI, G.: *Pruritus Cutaneus Universalis mit Urticariellem und Scharlachahnlichem Exanthem nach Atophan-gebrauch*, Cor.-Bl. f. Schweiz. Aerzte, 1915, xlv, 624-626.
- ³¹BRAMMER, M.: *Et Tilfaelde af Atophan-exanтем*, Ugeskr. f. Laeger, 1915, lxxvii, 1065.
- ³²KISSMEYER, A.: *Et Tilfaelde af Atophan-exanтем*, Ugeskr. f. Laeger, 1915, lxxvii, 792.
- ³³THOMSEN, H.: *Et Tilfaelde af Atophan-exanтем*, Ugeskr. f. Laeger, 1915, lxxvii, 894.
- ³⁴SCULLY, F. J.: *Idiosyncrasy to cinchophen*, Jr. Am. Med. Assoc., 1923, lxxxii, 623-624.
- ³⁵BARRON, M.: *Cinchophen poisoning; report of case with severe allergic reaction*, Jr. Am. Med. Assoc., 1924, lxxxii, 2010-2011.
- ³⁶BOOTS, R. H., and MILLER, C. P.: *Study of neocinchophen in treatment of rheumatic fever*, Jr. Am. Med. Assoc., 1924, lxxxii, 1028-1036.
- ³⁷SCHILLING, F.: *Unerwünschte Nebenwirkungen des Atophan*, Münch. med. Wchnschr., 1926, lxxiii, 362-364.
- ³⁸FINK, A. I.: *Cinchophen poisoning in allergic individuals; report of 2 cases*, Jr. Allergy, 1930, i, 280-282.
- ³⁹MILLER, T. H.: *Case of urticaria and toxic erythema following administration of mono-iodo-cinchophen*, Jr. Am. Med. Assoc., 1931, xcvi, 772-773.
- ⁴⁰EIMER, K.: *Atophanvergiftung und ihre Behandlung*, Deutsch. med. Wchnschr., 1931, lvii, 1663-1664.
- ⁴¹Bureau of Investigation: *Renton's hydrocin tablets; cinchophen sold as a "patent medicine" at a fancy price*, Jr. Am. Med. Assoc., 1931, xcvi, 209-210.
- ⁴²ORIEL, G. H., and BARBER, H. W.: *Proteose in urine, excreted in anaphylactic and allergic conditions*, Lancet, 1930, ii, 231-237.
- ⁴³NEYMANN, C. A., and OSBORNE, S. L.: *Treatment of dementia paralytica with hyperpyrexia produced by diathermy*, Jr. Am. Med. Assoc., 1931, xcvi, 7-13.
- ⁴⁴COCA, A. F., in TICE, F.: *Practice of medicine*, vol. 1, 1923, W. F. Prior and Co., Hagerstown, Md., p. 158.
- ⁴⁵MENNINGER, W. C.: *Skin eruptions with phenobarbital (luminal)*, Jr. Am. Med. Assoc., 1928, xci, 14-18.
- ⁴⁶ROSENTHAL, S. M., and WHITE, E. C.: *Clinical application of the bromsulfalein test for hepatic function*, Jr. Am. Med. Assoc., 1925, lxxxiv, 1112-1114.
- ⁴⁷FOLEY, E. F.: *Clinical value of tests of liver function*, Arch. Int. Med., 1930, xlv, 302-314.
- ⁴⁸SERBY, A. M., and BLOCH, L.: *Liver function as determined by bromsulfalein in 76 cases*, Am. Jr. Med. Sci., 1928, clxxvi, 367-383.
- ⁴⁹CORNELL, V. H.: *Bromsulfalein hepatic function test; report of series of tests*, Arch. Int. Med., 1929, xlv, 818-833.
- ⁵⁰GECKELER, E. O., and VISCHER, C. V.: *Use of mono-iodo-cinchophen in treatment of chronic arthritis*, Hahneman. Monthly, 1930, lxv, 358-360.
- ⁵¹ROSS, J. G.: *Résumé of results observed in treatment of arthritic and rheumatoid conditions*, Med. Jr. and Rec., 1930, cxxxii, 555-557.
- ⁵²RACKEMANN, F. M.: *Clinical allergy particularly asthma and hay fever, mechanism and treatment*, 1931, Macmillan Co., New York, p. 583.
- ⁵³LANDSTEINER, K.: *Experiments on anaphylaxis to azoproteins*, Jr. Exper. Med., 1924, xxxix, 631-637.
- ⁵⁴ZINSSER, H.: *Resistance to infectious diseases*, 1931, Macmillan Co., New York, pp. 446-448.

A Comparative Study of the Choloretic Effect of Bile Salts and Oleic Acid and Bile Salts*†

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FOR the past year we have employed a mixture of oleic acid and bile salts for the treatment of patients suffering from various forms of gall-bladder disease. The results obtained, which were reported elsewhere¹⁵ were gratifying in a large number of cases. We then decided to undertake an experimental study of the choloretic effect of bile salts and of oleic acid with bile salts to ascertain whether oleic acid which has a direct action on the gall-bladder also enhances the well known choloretic effect of bile salts. Theoretically, as will be shown later, it appeared plausible that such would be the case. Dr. A. C. Ivy, in a communication to one of us (E.W.L.), encouraged the undertaking of this problem and referred to certain known factors by which he indicated the final outcome of the experiment.

Before proceeding, it is important to define the terms "choloretic" and "cholagogue". The two terms are not interchangeable. The term "choloretic" is applied to a substance that is capable of stimulating bile formation by the liver and its excretion from the liver.

The term "cholagogue" is used to describe a substance which stimulates the expulsion of bile through the bile passages and gall-bladder.

METHOD OF PROCEDURE

Thirty patients were used for this experiment, 18 women and 12 men, of ages between thirty and fifty years. Of these patients, eight suffered from chronic cholecystitis, two from cholelithiasis, four from duodenal ulcer, two from cholangitis and one from gastric ulcer. The remaining 13 patients on examination showed no gastrointestinal or gall-bladder disease and were admitted to the hospital for other conditions. Each patient was subjected to biliary drainages on three different days. The drainages were conducted over a period of three hours each day. On the first day no stimulation was used, on the second day bile salts were used and on the third day a mixture of oleic acid and bile salts was used. In this manner we were able to compare the quantities of bile collected in a definite period each day.

The Jutte duodenal tube was uniformly used in these experiments. This tube has a small metal tip, which facilitates its passage through the pylorus

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into the duodenum. It also has a number of perforations for a distance of about two inches at its distal end, thus permitting a more thorough collection of the duodenal contents than is possible with any other tube. To further minimize the possible loss of duodenal contents, the patient was kept in a modified Trendelenberg position throughout the three hour period. The position of the tube in each instance was ascertained by fluoroscopic observation. The time required for the passage of the tube with some manipulation under the fluoroscope was from ten to thirty minutes.

As soon as the tube was in the second portion of the duodenum, ten cubic centimeters of warm water were administered through it and the tube clamped off for a period of ten minutes, after which time it was connected to a drainage bottle and the duodenal contents collected for one hour. Then, second and third hourly specimens were collected separately in a similar manner. No suction was used. On the second day the same procedure was followed, but three grains of bile salts (sodium glycocholate and sodium taurocholate in equal parts) were dissolved in the ten cubic centimeters of warm water. On the third day, with the same procedure, six cubic centimeters of oleic acid, together with three grains of bile salts, were administered through the tube. In 10 of the 30 cases only two cubic centimeters of oleic acid were used with three grains of bile salts.

RESULTS

As shown by table 1, 17 of the 30 experiments showed that there was a

definite increase in the quantity of bile collected on the second day when bile salts were used to stimulate biliary secretion. The lowest increase was 13 per cent, and the highest 180 per cent, the average being 91.4 per cent. On the third day of the experiment when oleic acid was combined with the bile salts, there was a definite increase of bile collected during the three hour period in 25 of the 30 patients experimented upon. The lowest increase at this time was 17 per cent and the highest 444 per cent. The average increase amounted to 143.6 per cent. Increases less than 25 cubic centimeters were not included in these figures.

Gall-bladder bile, or so-called B-bile, was not obtained on the first and second days when only water and bile salts were used as stimulants. On the third day when oleic acid and the bile salts were injected into the duodenum, a dark heavy bile, B-bile, was recovered in all instances with the exception of the cases of two patients whose gall-bladders had previously been removed. The gall-bladder bile, or B-bile, recovered amounted to between 35 and 45 cubic centimeters and in each instance appeared from two to five minutes after the administration of the oleic acid and bile salts through the duodenal tube. In this connection, it is interesting to note that Lyon et al¹, in similar experiments employing sodium dehydrocholate, have reported that they have observed that this substance inhibits the gall-bladder emptying function.

As a general rule, the bile recovered on the third day of the experiment, throughout the entire three hour period, contained an increased amount of

TABLE I

SHOWING AMOUNTS OF BILE COLLECTED ON THE THREE RESPECTIVE DAYS AND QUANTITIES OF OLEIC ACID USED, AND PERCENTAGE INCREASE IN DIFFERENT SUBJECTS

Case No.	1st day No stim- ulation	2nd day Bile Salts*		3rd day Oleic Acid and Bile Salts*		Remarks
	3 hour quantity	3 hour quantity	Percentage increase	3 hour quantity	Percentage increase	
1	132 c.c.	159 c.c.	20	240 c.c.	51	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
2	247 c.c.	227 c.c.	0	252 c.c.	0	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
3	290 c.c.	240 c.c.	0	443 c.c.	39	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
4	250 c.c.	99 c.c.	0	468 c.c.	71	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
5	121 c.c.	165 c.c.	36	545 c.c.	317	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
6	41 c.c.	10 c.c.	0	162 c.c.	197	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
7	204 c.c.	159 c.c.	0	280 c.c.	17	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
8	55 c.c.	35 c.c.	0	233 c.c.	250	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
9	116 c.c.	259 c.c.	123	294 c.c.	110	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
10	203 c.c.	122 c.c.	0	430 c.c.	92	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
11	97 c.c.	263 c.c.	171	217 c.c.	82	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
12	80 c.c.	224 c.c.	180	335 c.c.	268	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
13	120 c.c.	141 c.c.	0	263 c.c.	85	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
14	93 c.c.	240 c.c.	158	447 c.c.	338	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
15	610 c.c.	888 c.c.	45	1047 c.c.	71	Patient cholecystecto- mized.
16	275 c.c.	384 c.c.	39	568 c.c.	92	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
17	262 c.c.	180 c.c.	0	385 c.c.	31	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
18	136 c.c.	360 c.c.	164	133 c.c.	0	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
19	125 c.c.	304 c.c.	143	469 c.c.	243	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
20	0	112 c.c.	112	238 c.c.	238	B bile obtained on 3rd day. 6 c.c. Oleic acid used.

TABLE I—Continued

Case No.	1st day No stimulation	2nd day Bile Salts		3rd day Oleic Acid and Bile Salts*		Remarks
	3 hour quantity	3 hour quantity	Percentage increase	3 hour quantity	Percentage increase	
21	120 c.c.	196 c.c.	63	311 c.c.	125	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
22	532 c.c.	940 c.c.	76	748 c.c.	40	Patient cholecystectomized.
23	207 c.c.	304 c.c.	46	432 c.c.	89	B bile obtained on 3rd day. 6 c.c. Oleic acid used.
24	193 c.c.	219 c.c.	13	346 c.c.	58	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
25	96 c.c.	58 c.c.	0	197 c.c.	63	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
26	227 c.c.	309 c.c.	36	246 c.c.	0	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
27	77 c.c.	177 c.c.	129	255 c.c.	179	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
28	35 c.c.	180 c.c.	0	190 c.c.	0	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
29	45 c.c.	53 c.c.	0	285 c.c.	444	B bile obtained on 3rd day. 2 c.c. Oleic acid used.
30	270 c.c.	120 c.c.	0	185 c.c.	0	B bile obtained on 3rd day. 2 c.c. Oleic acid used.

* Note: In making calculations for the percentage increase on the third day, 40 c.c. have been deducted in each instance (except in cholecystectomized cases), so as not to include this amount which we found was the average quantity recovered from the gall-bladder.

bilirubin as shown by table 2 and also accordingly appeared to be much darker in color than the bile recovered during the similar period on the first two days. Ivy, in his Harvey lecture, New York City, on February 18, 1932, demonstrated that the gall-bladder does not empty at once when stimulated by cholecystokinin. Evidently a similar result follows when oleic acid is used as a gall-bladder stimulant and this may be the reason for the continued presence of darker bile in the three hourly specimens on the third day of the experiment.

In 10 subjects where only two cubic centimeters of oleic acid were used,

the quantities of bile recovered did not average any marked difference from those obtained where six cubic centimeters of oleic acid were used. B-bile appeared within the same period of time, thus demonstrating the marked cholagogue action of even small quantities of oleic acid.

Chart 1 shows graphically the response obtained on the second and third days when bile salts alone and oleic acid with bile salts, respectively, were used as compared with the first day of the experiment when only water was used. An analysis of the curves readily proves that the response to stimulation on the third day was

TABLE II
CHANGES IN THE CHEMICAL AND PHYSICAL PROPERTIES OF THE BILE, ON THE FIRST, SECOND AND THIRD DAYS RESPECTIVELY

Case No.	First day—three hours					Second day—three hours					Third day—three hours					
	Volume—c.c.	Total Solids	Specific Gravity	Cholesterol, mg. per cent	Bilirubin, mg. per cent	Volume—c.c.	Total Solids	Specific Gravity	Cholesterol, mg. per cent	Bilirubin, mg. per cent	Volume—c.c.	Total Solids	Specific Gravity	Cholesterol, mg. per cent	Bilirubin, mg. per cent	
1	132	1.16	1.008	78.4	6.7	159	1.4	1.007	79.7	3.95	240	1.3	1.009	79.2	10.9	
2	247	1.2	1.006	83.0	4.4	227	1.6	1.007	13.3	4.0	252	1.3	1.008	23.3	4.3	
3	290	1.6	1.008	74.9	12.3	240	1.5	1.008	124.	2.9	443	1.1	1.009	52.5	3.4	
4	250	1.4	1.008	55.7	6.7	99	1.5	1.007	14.6	0.33	468	1.2	1.010	118.	12.7	
5	121	1.1	1.006	88.0	2.3	165	1.3	1.005	55.5	1.8	545	1.3	1.009	89.3	2.6	
6	41	1.0	1.009	72.0	1.4	10	Insufficient quantity for determination					162	1.4	1.010	81.6	5.5
7	204	1.4	1.008	31.2	0.3	159	1.2	1.009	23.0	0.8	280	1.5	1.012	101.	9.6	
8	55	1.6	1.010	57.4	3.0	35	1.4	1.009	58.8	5.0	233	1.8	1.011	81.6	21.9	
9	116	1.3	1.008	30.0	2.1	259	1.0	1.008	34.0	2.3	294	1.4	1.010	44.0	11.8	
10	203	1.3	1.007	48.3	6.3	122	1.5	1.007	70.0	5.5	430	1.6	1.009	40.0	5.6	
11	125	1.4	1.009	32.0	1.5	304	1.7	1.011	44.0	3.8	469	2.0	1.012	68.0	8.0	
12	120	1.1	1.009	41.6	4.0	196	1.0	1.009	37.6	2.0	311	2.1	1.011	69.3	15.6	
13	532	1.2	1.009	55.6	2.5	940	1.4	1.009	53.3	1.8	748	1.0	1.009	49.4	1.5	

CHART I

SHOWING COMPOSITE CURVES OF THE AMOUNTS OF BILE COLLECTED ON THE FIRST, SECOND AND THIRD DAYS RESPECTIVELY

C.C. BILE COLLECTED

180

160

140

120

100

80

60

40

20

Hours 1/2 1 1 1/2 2 2 1/2 3

----- REPRESENTS 1ST DAY (NO STIMULATION)
 - - - - - REPRESENTS 2ND DAY (BILE SALTS STIMULATION)
 ——— REPRESENTS 3RD DAY (OLEIC ACID AND BILE SALTS STIMULATION)

prompt, the largest hourly quantity being obtained within the first hour.

Table 2 shows some of the chemical and physical changes that occurred in the bile on the different days of the experiment. These figures are the averages for each of the three hour periods. Actually, the bile recovered

during each hour was tested separately and as a rule the dark, heavy B-bile, usually recovered during the first hour after the administration of oleic acid with bile salts on the third day, showed the highest figures in the cholesterol and bilirubin contents.

The specific gravity and total solids

were estimated in each of the specimens. These figures are of little value because of the cellular matter and duodenal debris found in bile obtained by the transduodenal method.

DISCUSSION

The fact that oleic acid causes the gall-bladder to contract and to empty has been amply demonstrated by the experiments of Copher and Kodama², Whitaker³, and Ivy⁴. Ivy and Oldberg⁵ have proved that a fatty acid coming in contact with the duodenal mucosa stimulates the formation of a hormone which causes the gall-bladder to contract and to expel most of its contents. They named this hormone "cholecystokinin". This work has recently been confirmed by Crandall.⁶ One of us (E. W. L.⁷) has shown roentgenologically, that five cubic centimeters of oleic acid, taken orally, will likewise cause a gall-bladder to expel most of its contents within two or three hours. Further work has shown that a similar result may be accomplished with the administration of two cubic centimeters of oleic acid. Stewart and Ryan,⁸ working with various drugs, corroborated these results only when oleic acid was used.

The choleric effect of bile salts has been amply proved by the physiologists of the latter part of the nineteenth and early part of the twentieth centuries. The literature is replete with evidence that the stimulating effect of bile salts upon the liver cells causes an increased production of bile.

Bayliss and Starling⁹ proved a number of years ago that the intravenous injection of secretin not only caused a copious secretion of pancreatic juice,

but also doubled the rate of flow of bile from the liver. Mellanby¹⁰ has shown that secretin stimulates bile formation indirectly by its action on the pancreas, i.e., pancreatic stimulation reflexly stimulates the liver. If the animal is depancreatized, injections of secretin fail to increase the flow of bile from the liver. Ivy¹¹ has shown that oleic acid stimulates the flow of pancreatic juice through an hormonal action. When oleic acid comes in contact with the duodenal mucosa it activates the production of secretin. In the light of the above knowledge it occurred to us that oleic acid should have a choleric effect. Our present study confirms this conclusion.

As to the method of recovering the bile, we find that our results compare favorably with the quantities shown in similar work done by Wakefield and his co-workers¹², on a group of six cases. The average amount of bile they recovered through the duodenal tube in a half-hour period, without stimulation, was 21.2 cubic centimeters. In our group of 30 cases the average half-hourly output, without stimulation, was 30.8 cubic centimeters. Following stimulation they found the average return of bile was 55.6 cubic centimeters per half hour. Our results show 59.1 cubic centimeters in the same period of time, with oleic acid and bile salts stimulation. McClure, Wetmore, and Reynolds¹³ believe that much of the bile excreted into the duodenum is lost because of the normal downward peristalsis and accordingly cannot be recovered by means of the duodenal tube. Okada et al ¹⁴ have concluded that 94 to 99 per cent of duodenal contents is re-

covered through the tube. While we cannot with reasonable certainty say what percentage of contents is actually recovered, we are inclined to concur with the opinion of the latter authors, judging by the relatively uniform quantities we recovered from individual subjects on the different days. There is no evidence in our results of daily gross fluctuations; only increases in quantities that were due to stimulation were noticed. In fact, after noting the quantities collected on the first and second days, we were able to predict approximately the results of the last day's draining. We believe that the patient's position during the drainage period and the type of tube used are factors of considerable importance. It does not seem plausible to assume that by virtue of some unknown coincidental factors, more bile found its way through the duodenal tube on the third day of the experiment, to give us persistent increased quantities in 83 per cent of our cases.

SUMMARY AND CONCLUSIONS

The comparative choleretic effect of bile salts and oleic acid and bile salts has been studied in a group of 30 subjects. In each case the bile was collected by means of a duodenal tube on three different days for three hourly periods. The first day served as a control day, when no stimulation was employed. On the second day three grains of bile salts were used for stimulation, and on the third day three grains of bile salts plus six cubic centimeters of oleic acid were used. In ten subjects, only two centimeters of oleic acid were used with three grains

of bile salts, to detect any possible alteration in the results obtained. The detailed technic is described. The quantities of bile drained on each day were noted, and examinations of the different samples of bile were made for possible chemical or physical changes. Less than 25 cubic centimeters was not considered a sufficient quantity to be accepted as an increase.

The following results were obtained:

1. In 17 patients, the quantity of bile collected was increased on the second day when bile salts stimulation was used. The lowest increase was 13 per cent, the highest 180 per cent, the average amounting to 91.4 per cent.

2. In 25 patients, the bile collected on the third day was increased when oleic acid and bile salts were used. The lowest increase was 17 per cent, the highest 444 per cent, the average increase amounting to 143.6 per cent. The ten cases receiving the smaller amount of oleic acid did not show any appreciable difference in the quantity of bile excreted, and were included in the above figures. Gall-bladder bile was obtained in every instance on the day when oleic acid had been used, with the exception of two cholecystectomized cases. The average quantity of this bile recovered was about 40 cubic centimeters.

3. Figure 1 shows graphically the response obtained after stimulation on the second and third days.

4. While some chemical and physical changes were noted in the different samples of bile, it is difficult to draw definite conclusions in view of the fact that the bile was obtained transduodenally.

As a result of this study, it may be concluded that oleic acid even in small quantities is not only a potent cholagogue but also definitely enhances the choleretic effect of bile salts.

We wish to acknowledge our thanks to Dr. Maurice Vaisberg and Dr. Harry Sherman for their kind assistance in these experiments, and to Mr. Kurt Heinhold for the chemical analysis of the various specimens.

BIBLIOGRAPHY

- ¹STERNER, R. F., BARTLE, H. J., and LYON, B. B. V.: The cholagogue effect of the intravenous injection of sodium dehydrocholate, with résumé of literature on bile salt metabolism, *Am. Jr. Med. Sci.*, 1931, clxxxii, 822-839.
- ²COPHER, G. H., and KODAMA, S.: The regulation of the flow of bile and pancreatic juice into the duodenum, *Arch. Int. Med.*, 1926, xxxviii, 647-653.
- ³WHITAKER, L. R.: Diagnosis of gall-bladder disease: application of recent advances in physiology, *Jr. Am. Med. Assoc.*, 1927, lxxxviii, 1791-1796.
- ⁴IVY, A. C.: Hormone mechanism of gall-bladder contraction and evacuation, *Am. Jr. Surg.*, 1929, vii, 455-459.
- ⁵IVY, A. C., and OLDBERG, E.: Hormone mechanism for gall-bladder contraction and evacuation, *Am. Jr. Physiol.*, 1928, lxxxvi, 599-613.
- ⁶CRANDALL, L. A., JR.: Mechanisms of the contraction and evacuation of the gall-bladder, *Arch. Int. Med.*, 1931, xlviii, 1217-1224.
- ⁷LIPSCHUTZ, E. W.: A new diagnostic and therapeutic aid in biliary tract disease, *Med. Jr. and Rec.*, 1927, cxxv, 321-322.
- ⁸STEWART, W. H., and RYAN, E. J.: Cholecystographic studies after administration of some of the popular cholagogues, *Am. Jr. Roentgenol. and Radium Therap.*, 1928, xix, 341-343.
- ⁹BAYLISS, W. M., and STARLING, E. H.: The mechanism of pancreatic secretion, *Jr. Physiol.*, 1902, xxviii, 325-353.
- ¹⁰MELLANBY, J.: Bile salts and secretin as cholagogues, *Jr. Physiol.*, 1928, lxiv, 331-340.
- ¹¹IVY, A. C.: Newer physiology of the gastrointestinal tract, *Am. Jr. Med. Sci.*, 1927, clxxiii, 453-460.
- ¹²WAKEFIELD, E. G., POWELSON, H. P., and McVICAR, C.S.: The use of a sodium salt of dehydrocholeic acid (decholin) as a choleretic, *ANN. INT. MED.*, 1929, iii, 572-577.
- ¹³McCLURE, C. W., WETMORE, A. S., and REYNOLDS, L.: Physical characters and enzymatic activities of duodenal contents; findings during gastric digestion in normal young men, *Jr. Am. Med. Assoc.*, 1921, lxxvii, 1468-1469.
- ¹⁴OKADA, S., SAKURAI, E., IMAZU, T., and KURAMOUCHI, K.: Pancreatic function; quantitative estimation of pancreatic secretion, *Arch. Int. Med.*, 1928, xlii, 270-281.
- ¹⁵FINKELSTEIN, R., and LIPSCHUTZ, S. W.: Final report on the therapeutic effect of oleic acid and bile salts in gall-bladder disease, *Clin. Med. and Surg.*, 1933, xl, 78-80.

Lobar Pneumonia*†

A Report of 2039 Cases

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FROM January 1, 1916, to December 31, 1931, inclusive, 2039 cases of lobar pneumonia were observed in the Memphis General Hospital. Of this number, 517 occurred in white patients and 1522 in negroes. During this same period, the white patients comprised approximately one-third of the total discharges from the hospital but only one-fourth of the total number with pneumonia.

INCIDENCE

The morbidity of pneumonia, according to Blake,¹ depends upon the pathogenic properties of the organism, the opportunities for infection, and the factors of susceptibility and resistance. Since neither the Memphis City Board of Health nor the Tennessee State Board makes pneumonia a reportable disease, it is impossible to ascertain its true local incidence. It is well known that the number of cases varies greatly from year to year in all localities. This fact is strikingly illustrated

in chart 1. During the sixteen years covered in this study, the lowest incidence was in 1920, with 44 cases, and the highest in 1931, with 304 cases (chart 5). Thus, in 1920 the 44 cases represented 1 per cent of the total discharges, whereas the 304 cases in 1931 represented 2.8 per cent (chart 1-a).

Institutional statistics such as these offer the only means of estimating the incidence of pneumonia other than mortality tables. Since, as will be shown later, the death rate also varies widely from year to year, these mortality tables give only an approximate idea of the number of cases. The discrepancy is illustrated in a comparison of the incidence and death rate at the Memphis General Hospital with the mortality for the City and State (charts 1, 2, 3, 5).

Chart 1 shows the relative incidence of pneumonia among the rural and urban population for the State of Tennessee. Except for 1918, when there was a sharp rise, probably because of the influenza epidemic, there was only a slight variation in the mortality among the rural white and negro population and but little more among the urban whites. On the other hand, the rate was much higher and more variable among the urban negroes.

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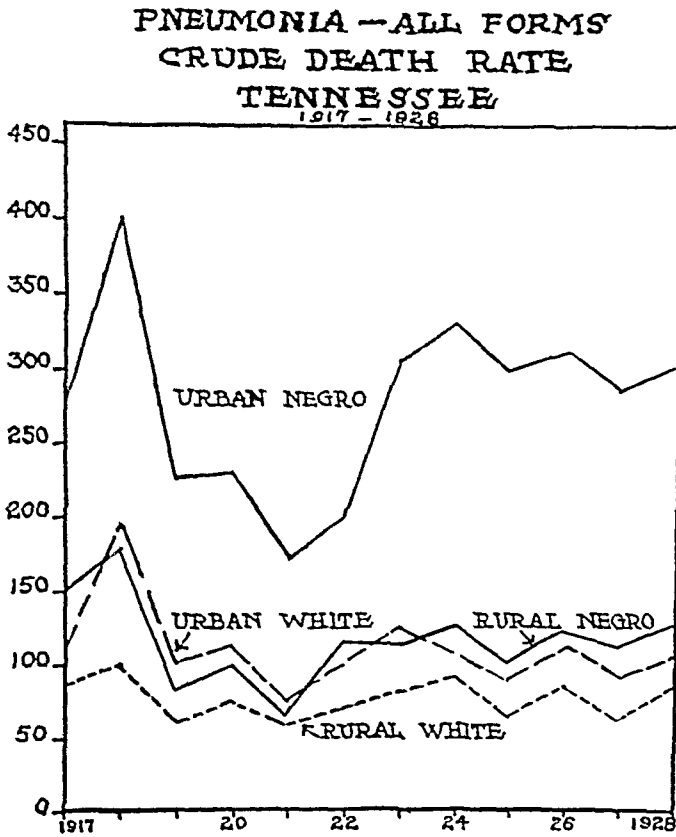


CHART 1

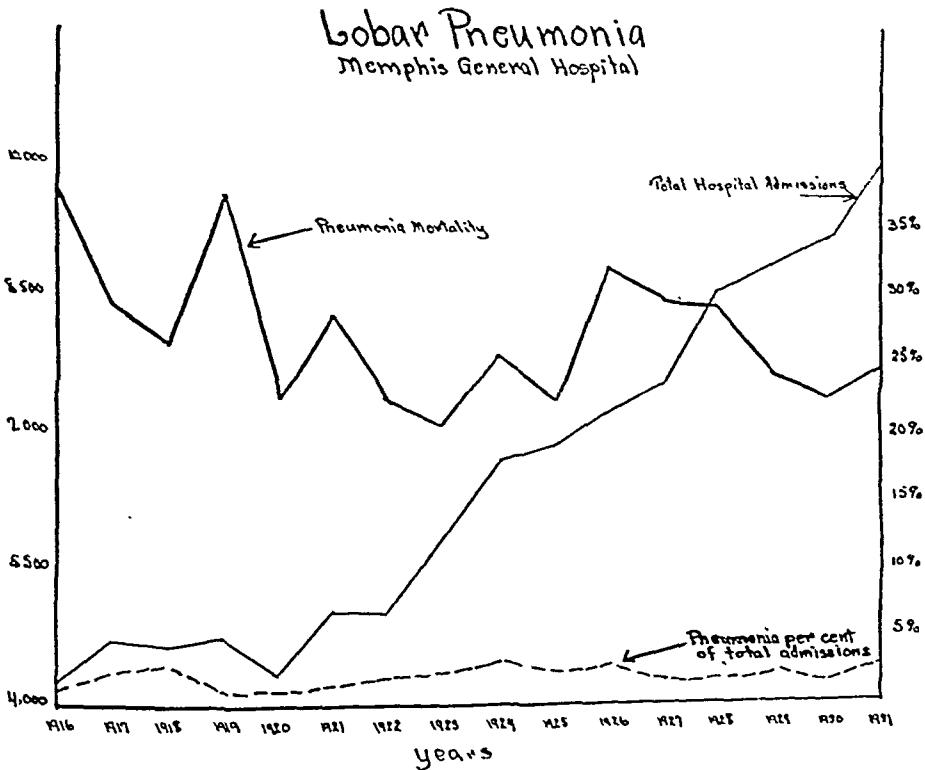


CHART 1-a

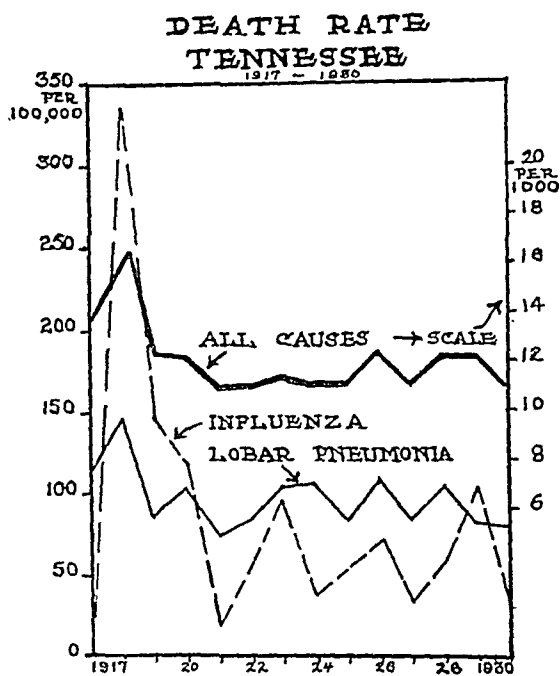


CHART 2

The crowded, unhygienic living conditions of the urban negroes account not only for the higher incidence, but also for the higher death rate.

The importance of meteorological conditions as predisposing factors in the occurrence of pneumonia cannot be doubted, yet no one has been able to define this relation satisfactorily. Chart 6 shows a comparison between the pneumonia deaths in the Memphis General Hospital and in the City of Memphis, and the precipitation, relative humidity, days of possible sunshine, and the average mean monthly temperature.² In this series, as in many similar studies, no constant relation could be found between any of

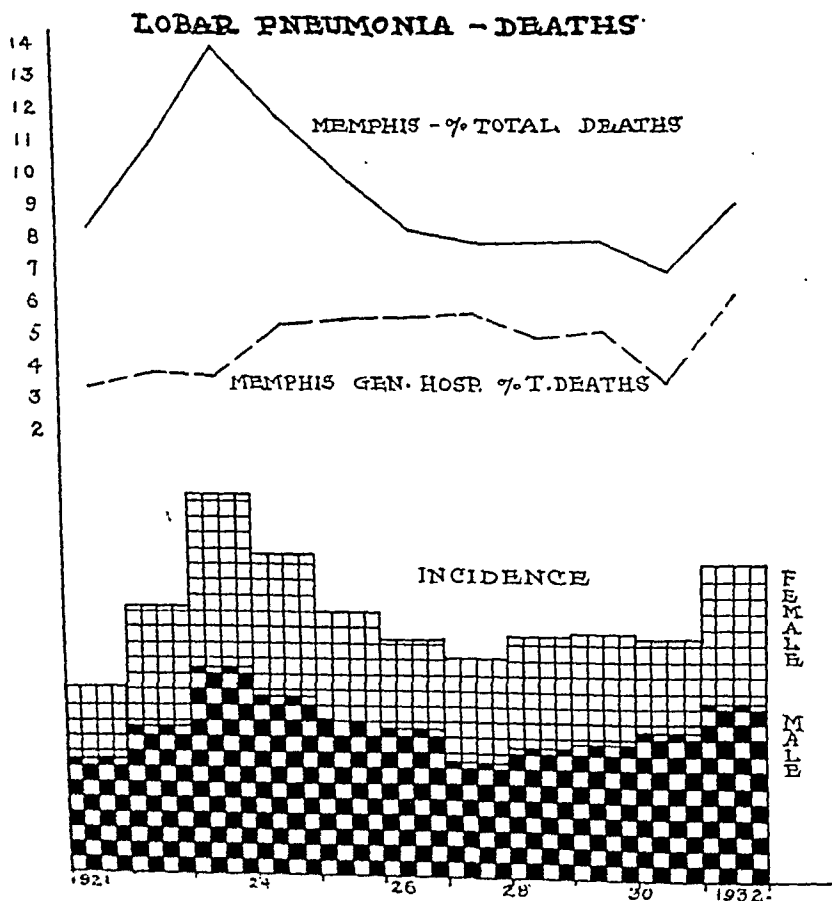


CHART 3

the meteorological influences and the pneumonia deaths.

Economic conditions may have some effect upon the incidence of pneumonia. In computing the ratio of

among men because of their occupational exposure, yet the fatalities among the men and women were almost equal in the City of Memphis from 1921 to 1931, inclusive.

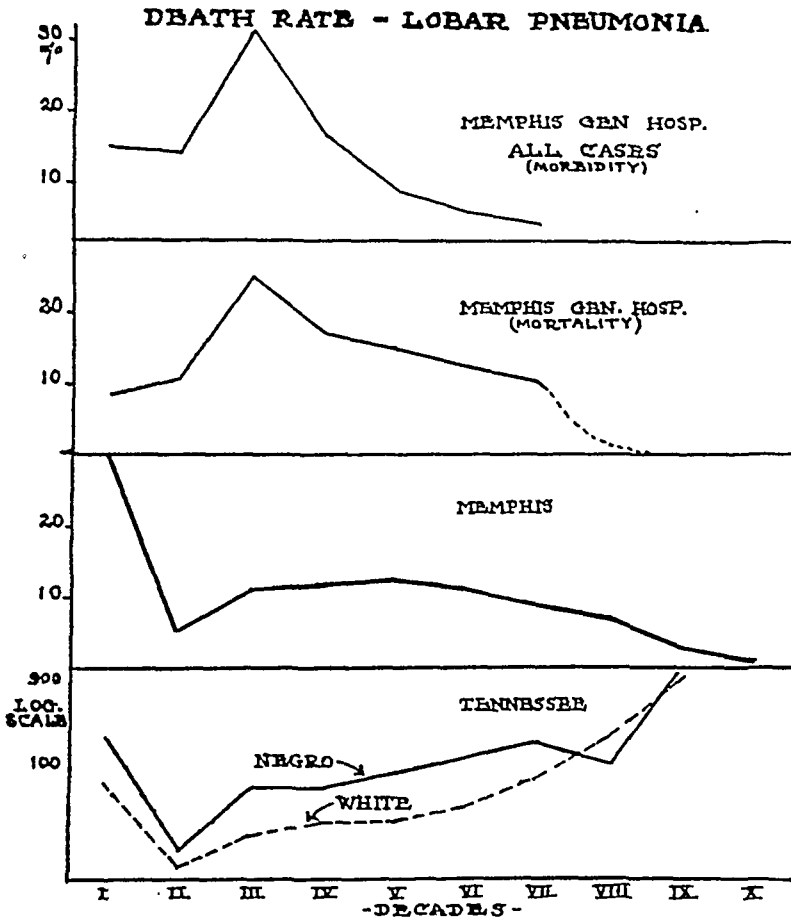


CHART 4

business failures per year³ with the pneumonia death rate in the City of Memphis, it was noted that the highest incidence of pneumonia seemed to follow the year of the greatest number of business failures. The comparison, however, is not sufficiently definite to be significant.

SEX

Usually the statement is made that lobar pneumonia is more prevalent

AGE

At what age do most cases of pneumonia occur? Of these 2039 patients, the majority were between twenty and forty years (chart 4). There seems to have been a marked discrepancy, however, between the age incidence and death rate at the General Hospital as compared with the mortality in the City of Memphis and State of Tennessee.^{4,5,6} The rising curve of the

death rate for lobar pneumonia after the fifth decade for the State undoubtedly means that many cases of lobular or terminal bronchopneumonia were included. The death rate for lobar pneumonia in the first decade in Memphis and Tennessee as reported is unusually high. Holt,⁷ in a study of 426 cases, found that over 90 per cent of

ally low, whereas in bronchiopneumonia, which is often secondary, it is always high, it is reasonable to assume that many cases reported as lobar were in reality bronchopneumonia.

PROGNOSTIC SIGNS

In the analysis of this series, an attempt was made to determine those

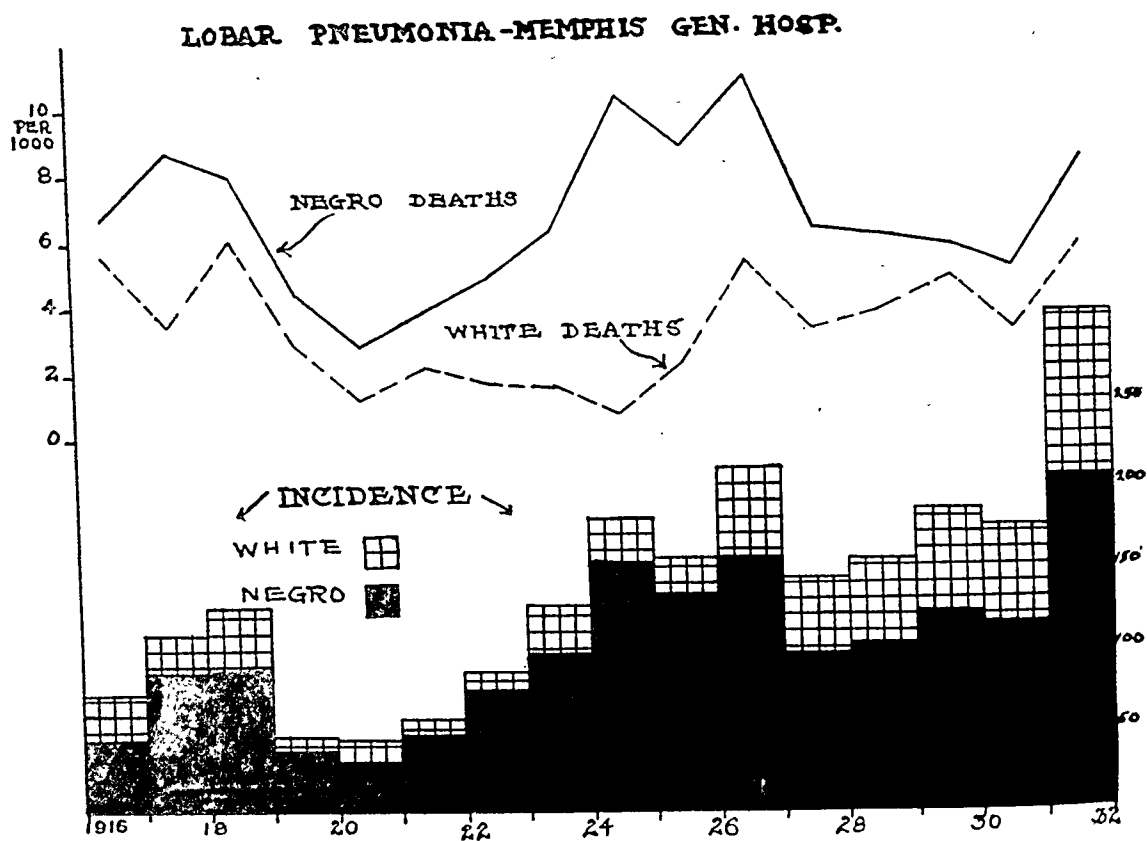


CHART 5

pneumonia which occurred in the first three years of life were bronchial in type. After the fourth year of life bronchopneumonia is more often secondary to some other condition. Of 3778 patients reported to the Memphis City Health Department as having died of lobar pneumonia, 1079, or almost one-third, were four years of age or under. Since the mortality from lobar pneumonia at this age is usu-

ally low, whereas in bronchiopneumonia, which is often secondary, it is always high, it is reasonable to assume that many cases reported as lobar were in reality bronchopneumonia.

data which would aid in predicting the most probable outcome of the average case. Many physicians have some particular sign or symptom upon which they rely for prognosis, while others maintain that it is almost impossible to foretell the course of any individual case. Loomis aptly stated, "There are some who have pneumonia whom we cannot cure, some whom we cannot kill, and some whom wise treatment

and good nursing will help to recover."

In the 2039 cases of lobar pneumonia of this series, the average height of the temperature, the systolic and diastolic blood pressure, the pulse pres-

a constant pulse rate of 120 or above as "toxic". Thus, pneumonia patients with a persistent tachycardia of 120 or over have a bad prognosis and require extraordinary care.

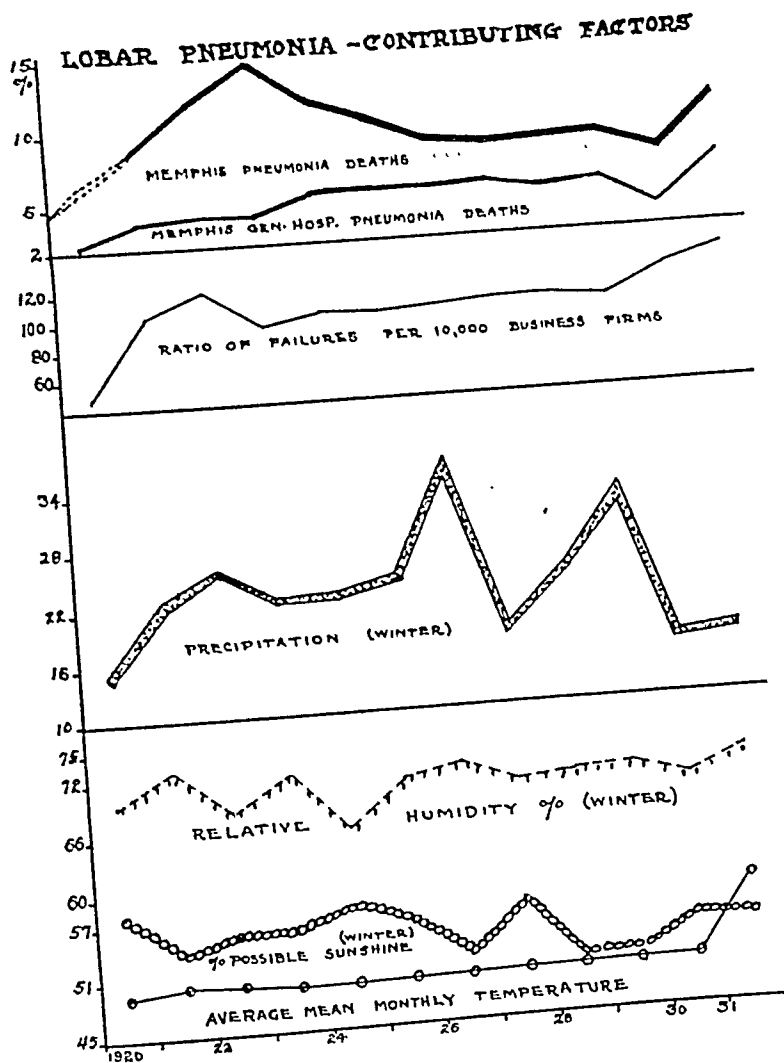


CHART 6

sure, and the urine tests varied but little between those who died and those who recovered (table 1). A persistently high pulse rate definitely stands out as a reliable indication of the severity of the disease. MacLachlan, Kastlin and Lynch⁸ confirm this and consider all cases of pneumonia with

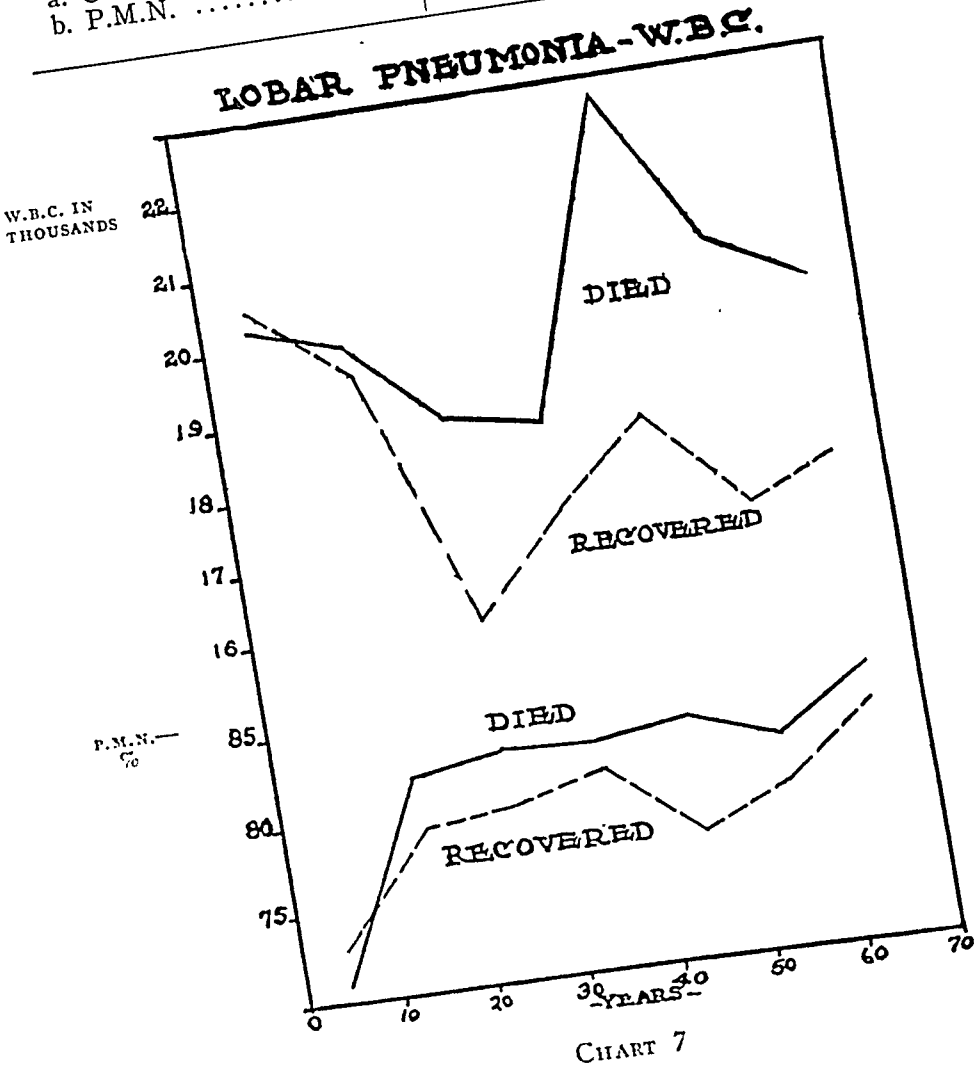
Leukocyte Count. Of what prognostic aid is the white blood cell count? In actual figures, there was little difference in the count of those who recovered and those who died (table 1). However, when a comparison is made of the white blood cell count, taking into consideration the age of the pa-

tient, it is significant that at the age of twenty years and above, those with a count of 18,500 or below lived,

whereas those with a count of above 18,500 died (chart 7). It must be understood that this is an average count

TABLE I
LOBAR PNEUMONIA, PROGNOSTIC SIGNS
(2039 cases)

	Cases Recovered	Cases Died
Average		
Temperature	101 degrees	102 degrees
Pulse	96	122
Blood pressure	108/61	110/63
Pulse pressure	47	47
Urine		
a. Albumin	38%	42%
b. Casts	18%	23%
White blood		
a. Cells	20,202	18,045
b. P.M.N.	82%	79%



and that some patients with a leukocytosis above this figure lived and some with a low count died. A very low leukocyte count signifies a poor response on the part of the patient and a bad prognosis. Finally, emphasis

mann test was 26 per cent, as compared with 27.1 per cent for the entire series. The difference is too slight to be significant.

Lobes Involved. A comparison of the involvement of the different lobes

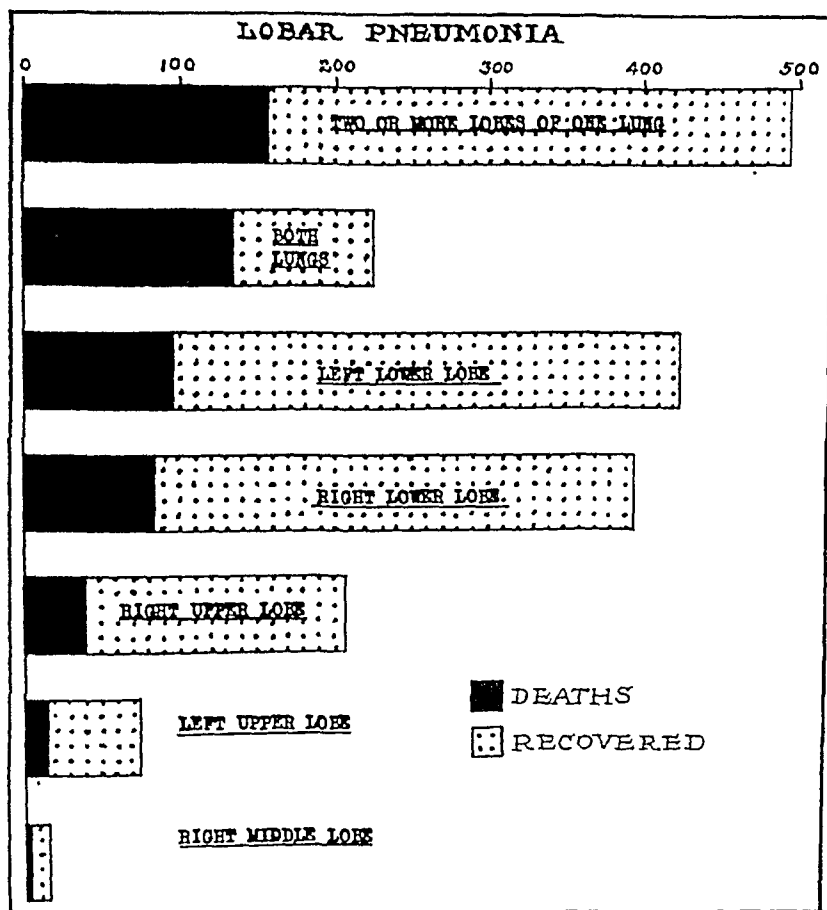


CHART 8

should be placed on the fact that, in this series, during the period of life when lobar pneumonia is most common (twenty to forty years), the majority of the patients with a white cell count above 18,500 died.

Syphilis. What effect does syphilis have on the prognosis in lobar pneumonia? In this group, 458 patients, or 22.4 per cent, gave a positive Wassermann test. The mortality rate for the number with a positive Wasser-

mann test was 26 per cent, as compared with 27.1 per cent for the entire series. The difference is too slight to be significant.

may be seen in chart 8. Two or more lobes were affected in almost one-fourth of the series. The mortality was higher when the disease was present in both lungs than when two or more lobes of one lung were involved. The lower lobes were involved more than twice as often as the upper, and the right lower more than twice as often as the right upper.

Blood Cultures. Blood cultures were made in 281 cases. In 90, or 32 per

cent, a positive culture was reported. The mortality among those with a positive culture was 52.2 per cent, as compared with 24.2 per cent for those with a negative culture (table 2).

Sputum. The sputum was studied in 574 cases. The laboratory reported a

of early adult life. In this series, the greatest number of cases of Type I, like those of Types II and III, occurred between the third and fourth decades (chart 9).

Previous Attacks. Three hundred and thirty-five patients, or 16.4 per

TABLE II
LOBAR PNEUMONIA—MEMPHIS GENERAL HOSPITAL
(2039 cases)

	No. of Cases	Number Died	Mortality	No. with Pos. Bl. Cult.	Number Died	Mortality
Type I	104	27	25.9%	31	14	45.1%
Type II	69	17	24.6%	10	9	90. %
Type III	73	21	28.7%	10	4	40. %
Type IV	180	38	21.2%	16	7	44.4%
Pneumococcus (not typed)	44	12	27.2%	14	7	50. %
Pneumococcus (2 types)	13	2	15.4%	2	2	100. %
Streptococcus	49	13	26.5%	7	4	57.1%
Mixed types	42	10	23.8%			
Total	574	140		90	47	
Average			24.2%			52.2%
Blood culture taken in 281 cases: 32% positive blood cultures						

streptococcus in 49 of this number, and seven of these showed a positive blood culture. Although clinically these were cases of lobar pneumonia, objection might be raised to their inclusion in the series. Of the 426 cases showing a single type of pneumococcus, 180 were Type IV, 104 Type I, 73 Type III, and 69 Type II (table 2). It was interesting to observe the marked variation from year to year in the relative incidence, as well as the mortality of the different types.

It is generally conceded that Type I lobar pneumonia is primarily a disease

cent, gave a history of one or more previous attacks of pneumonia. The mortality of this group was 22.6 per cent, as compared with 28.3 per cent for the remainder of the series (table 3). It is thought by some that one attack predisposes to a second, yet the fact that the mortality was less among those who had previous attacks would indicate a certain amount of lasting immunity.

COMPLICATIONS

In table 4 are listed the most important complications recorded in this series.

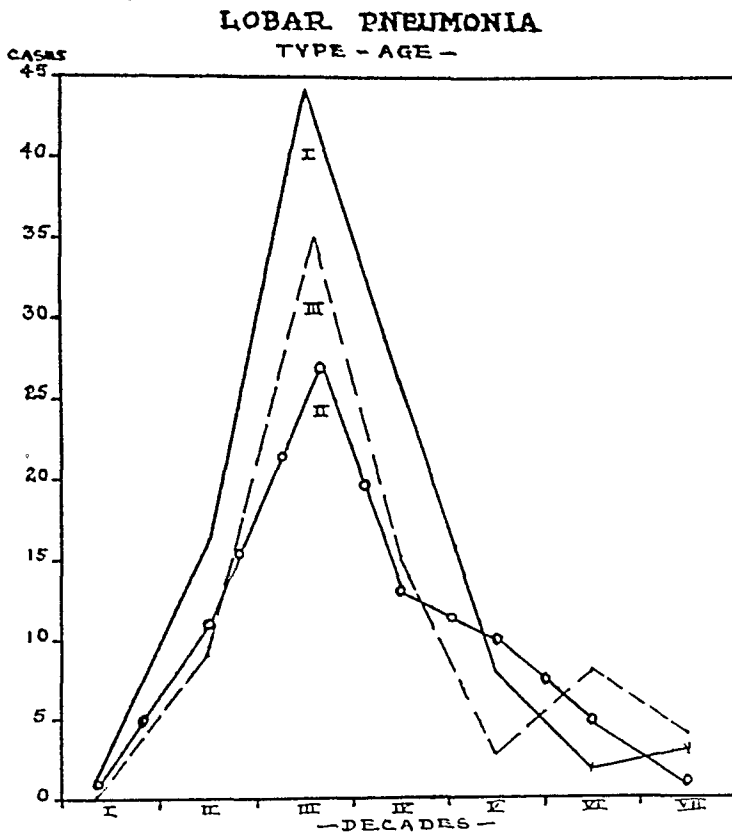


CHART 9

LOBAR PNEUMONIA - TREATMENT

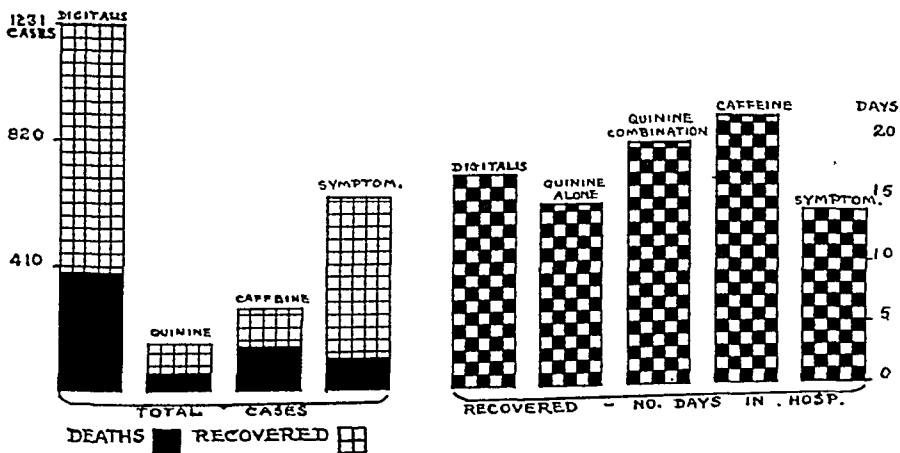


CHART 10

Empyema, as might be expected, ranks first. It developed in 53 cases, or 2.6 per cent of the entire number.

ably larger number of effusions would have been found. *Pericarditis* was mentioned in only

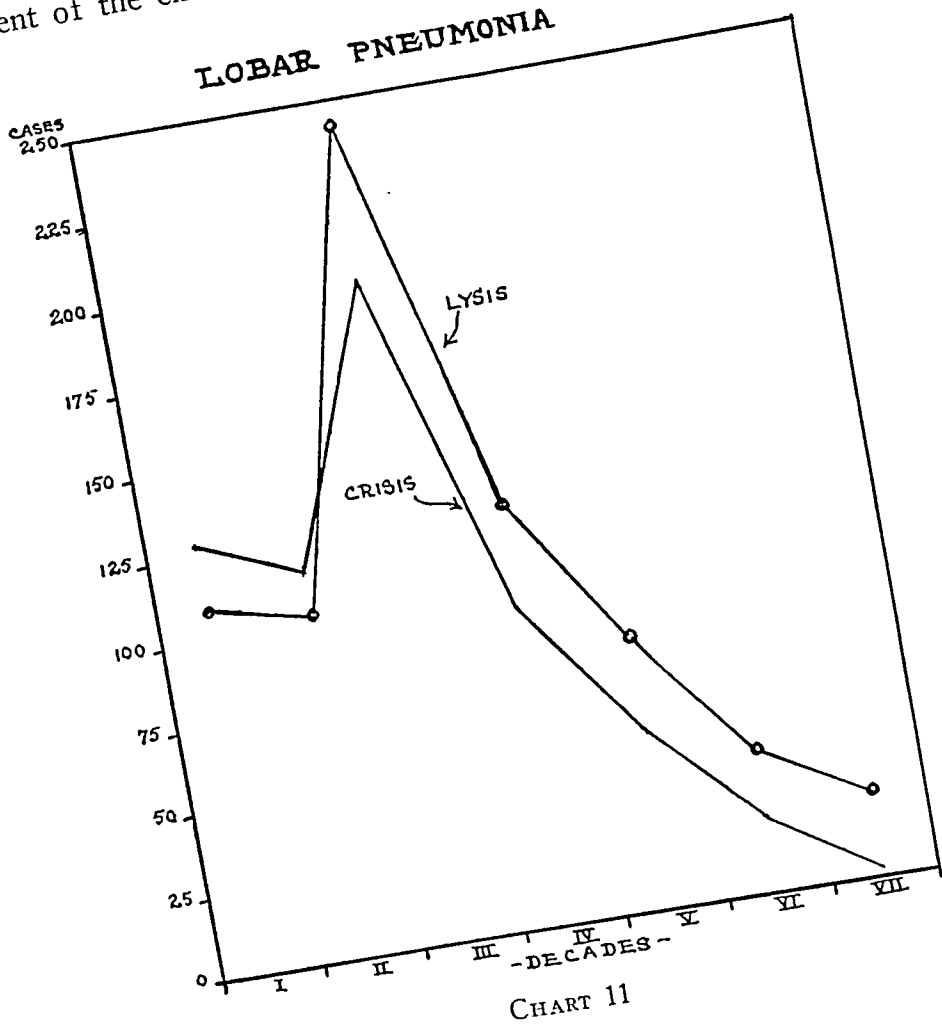


TABLE III
LOBAR PNEUMONIA — MEMPHIS GENERAL HOSPITAL
(2039 cases)

Summary	No. of Cases	No. of Deaths	Mortality
Pneumonia cases	2,039	554	27.1%
Present attack	1,704	483	28.3%
Previous attack	335	76	22.6%
Positive Wassermann	458	121	26. %

Pleural effusion, on the other hand, was recorded in only 8 cases. There is no doubt that if more exploratory aspirations had been made, a consider-

16 cases. Obviously, this is far too low. Autopsy records show that the incidence of pericarditis is second only to that of the pleural complications.

Doubtless it is overlooked more often than any other complication in pneumonia.

Multiple gastric ulcers complicated

treatment of this series of cases. The groups are too small to justify any conclusions for or against the use of any of these remedies. Nevertheless,

TABLE IV
LOBAR PNEUMONIA—MEMPHIS GENERAL HOSPITAL
(2039 cases)

Complications	Total Cases	Number Died	Mortality	Operative Mortality
Empyema	53	12	22.6%	19.3%
Lung abscess	9	5	44.4%	—
Pericarditis	16	13	81.2%	—
Endocarditis	4	2	50. %	—
Pleural effusion	8	1	12.5%	—
Otitis media	44	0	—	—
Mastoiditis	7	1	14.3%	25. %
Meningitis	35	33	94.2%	—
Delirium	86	64	74.4%	—
Paraplegia	1	1	100. %	—
Jaundice	34	15	44.1%	—
Peritonitis	5	4	80. %	100. %
Tuberculosis	27	13	48.1%	—
Supp. parotitis	1	0	—	—
Lymphadenitis	2	1	50. %	—
Thrombophlebitis	1	1	100. %	—
Subcut. abscess	10	2	20. %	—
Acute arthritis	4	2	50. %	—
Pregnancy-abortion	16	6	37.5%	—
Erysipelas	4	2	50. %	—
Epidemic parotitis	3	1	33.3%	—
Pyelo-nephritis	19	12	63.1%	—
Ulcers—one each (leg, rectum, gluteal skin and stomach)	4	1	25. %	—

one case. Death was caused by gastric hemorrhage, as shown at autopsy.

TREATMENT

In table 5 and chart 10 are listed the various remedies employed in the

it is interesting to consider the results obtained with some of the drugs most commonly employed.

Digitalis. It will be noted that digitalis alone or in combination with some other drug was used in 1231

cases. The average mortality for this group was 31.1 per cent. It was used alone in 745 cases, with a mortality of 22.5 per cent. The highest mortality, 58.2 per cent, occurred in the

Caffeine. Next to digitalis, caffeine seems to have been the most popular stimulant employed. It was used alone in 86 cases, one-half of whom died. When combined with some other

TABLE V
LOBAR PNEUMONIA—MEMPHIS GENERAL HOSPITAL
(2039 cases)

Treatment	Total Number Cases	Number Died	Mortality	Average Hosp. Stay of Those Who Recovered
Digitalis	745	168	22.5%	16.1 days
Dig. and quinine	128	38	29.6%	18.7 days
Dig. and caffeine	175	103	58.2%	21.1 days
Dig. and antiserum	15	7	46.6%	17.5 days
Dig. and pneu. antigen	55	13	23.6%	18.2 days
Dig. and strychnine	26	5	19.1%	12 days
Dig., caff. and quinine	36	20	55.5%	21.9 days
Dig., caffeine and strychnine	36	14	38.8%	17.3 days
Digitalis (alone or in combination)	1231	383	31.1%	17 days
Quinine	44	6	13.6%	14.8 days
Quinine (in some combination)	163	60	36.8%	19.5 days
Caffeine	86	43	50. %	22.3 days
Caffeine (in some combination)	271	154	56.8%	21.6 days
Antiserum	8	2	25. %	12.8 days
Pneumococcus antigen	12	3	25. %	11.1 days
None of the above drugs	636	112	17.6%	14 days
General average			27.1%	17.2 days

group in which digitalis was used in combination with caffeine. Although we did not compare the methods of treatment in 1916 with those of 1931, it is safe to say that digitalis was used routinely more often in 1916 than in recent years.

drug, the mortality was even higher, being 56.8 per cent. It should be stated, however, that this high death rate was not because of caffeine but in spite of it, since it was rarely given except when patients were desperately ill.

Quinine. Quinine was used in the third largest group. It was combined with some other drug in 163 cases, with a mortality of 36.8 per cent. Interestingly enough, the lowest mortality, 13.6 per cent, of any group was in the 44 cases in which quinine was used alone.

Symptomatic Treatment. The next most favorable group was the 636 cases treated symptomatically. In these the mortality was only 17.6 per cent. They were doubtless the mild cases, in contrast to the severe cases treated with caffeine and other stimulants.

Serum. The number who received pneumococcic serum and pneumococcic antigen was too small to warrant any conclusion.

According to popular opinion, pneumonia is a disease which ends by crisis, but in this series the numbers terminating by lysis and by crisis were almost equal (chart 11). The average age of those ending by crisis and lysis was 22 and 25 years, respectively. The ninth day was the average day of crisis in 616 cases in which the exact day could be determined. The average duration of the uncomplicated cases which ended by lysis was twenty-one days.

Considering the large proportion of negro patients at the Memphis General Hospital, an average mortality for pneumonia of 27.1 per cent over a period of sixteen years compares very favorably with statistics from large general hospitals in other sections. Dr. O. W. Bethea⁹ collected statistics from the Massachusetts General, Bellevue, St. Luke's, Garfield Memorial, Cook County, and the Charity Hospital and found that in 1915, of 2012 cases of

lobar pneumonia, the mortality was 32.3 per cent; in 1929, of 2489 cases, the average mortality was 40.4 per cent.

SUMMARY

1. An analysis has been made of 2039 cases of lobar pneumonia observed at the Memphis General Hospital from 1916 to 1931, inclusive.

2. A comparison has been made between the mortality rate for the hospital, the City, and the State.

3. The average mortality rate for the entire series was 27.1 per cent. In spite of the fact that the majority of these patients were negroes, the mortality rate compares favorably with published statistics from other municipal hospitals.

4. A comparison was made of the temperature, pulse rate, blood pressure, and blood count of those who died and those who recovered. No significant difference was found which would aid in the prognosis.

5. The mortality rate of those who gave a positive blood culture was 52.2 per cent, as compared with 24.2 per cent for those with a negative culture.

6. Digitalis was employed in 1231 cases, with a mortality rate of 31.1 per cent, as compared with an average of 27.1 per cent for the entire series and 17.6 per cent for those treated symptomatically.

7. Since lobar pneumonia is not a reportable disease in Tennessee, it is impossible to determine its true incidence or the mortality rate in private practice. There is reason to believe that the mortality rate for those cases treated in private homes is much less than these figures and other published statistics would indicate.

REFERENCES

- ¹BLAKE, F.: Harvard Alumni Magazine, 1931.
- ²Annual Meteorological Summary, U. S. Dept. of Agriculture, Weather Bureau, Memphis, Tenn., 1921-1931.
- ³R. G. Dun & Company Reference Book, 1921-1931.
- ⁴Tennessee Morbidity Statistics, State Department of Public Health, 1930.
- ⁵ELBRIDGE, S.: Differential mortality in Tennessee, Fisk Univ. Press, 1930.
- ⁶Tennessee Vital Statistics, State Department of Public Health, 1930.
- ⁷HOLT, L. E.: Diseases of infancy and childhood, 1924, D. Appleton & Company, New York and London, pp. 200-202.
- ⁸MACLACHLAN, W. W. G., KASTLIN, G. J., and LYNCH, R.: Use of dextrose in pneumonia, Am. Jr. Med. Sci., 1930, clxxix, 93-104.
- ⁹BETHEA, O. W.: Treatment of pneumonia, Jr. Am. Med. Assoc., 1930, xcv, 925-926.

Twins as Biologic Controls in the Study of Human Constitution*

An Additional Approach to the Study of Clinical Medicine

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WE physicians who have seen a veritable flood of new discoveries in science have become impressed by the importance of the environment in relation to human disease. The achievements in the field of bacteriology pointed to the identification of many of the infectious diseases, and in many instances led to the complete solution of the problem of contagion and of prevention. The fruitful researches in the study of nutrition, the phenomenal discovery of the vitamins, for example, pointed out factors hitherto unknown in the production of disease. As the web of information concerning the function of the endocrine glands is being untangled, we become aware of still another group of factors—thyroxin, insulin, adrenal substance—which take their place as agents through which physical disease may be understood.

So startling and so important have been these discoveries that of late there has been a tendency at large to think of the mechanism of disease entirely in terms of infection, of metabolic derangement, of neoplastic activity, or of physiologic dysfunction in one direction or another. Many of the

unsolved problems of disease will, indeed, be conquered when attacked from this approach, through researches in bacteriology, biochemistry and biophysics. Still, there are certain questions which remain unanswered, despite most precise objective methods of study. What, for example, is the meaning of "resistance" or "susceptibility" to disease? What underlies natural or racial immunity? Why of two individuals in the same environment, is one chosen for a specific disease and the other left untouched? What are the relative values of the two factors, the environmental and the individual, in the complex known as disease?

To be sure, the medical concept of disease has always been cognizant, in a general way, of the individual himself as a large factor. The element of human constitution in disease has been noted many times in many ways. Hippocrates' humoral theory classified individuals into the traditional sanguinous, choleric, melancholic and bilious tempers. Through the centuries clinicians have repeatedly been impressed by something of the individual's "diathesis" in its relation to his disease. We have long become

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familiar with such terms as "phthisic habitus," and "fair, fat and forty," which bear the hint of the relationship of physical structure to disease.

More recently, observers, particularly on the continent, have concerned themselves intensively with attempts to define more precisely the meaning of human constitution. Müller¹, Bauer², Borchardt³, and others have made illuminating contributions, in which one finds an attempt to integrate those basic factors inherent in the individual with those other interplaying elements in man's environment which culminate in disease. In America, the pioneer efforts thoroughly to study man in relation to his disease came from Draper⁴, who, beginning with a study of man's morphologic attributes, proceeded to investigate certain physiologic and psychologic aspects of the individual in an attempt to make something concrete of the concept of human constitution. His studies have yielded data of considerable importance. They have pointed to possibilities of correlating individuals of particular constitutional make-up with their disease susceptibilities. His work is of particular interest to the clinician in that it demonstrates a tendency of certain pathologic entities to occur with striking frequency in some groups, and with relative rarity in individuals "constituted" differently. Here, indeed, is a suggestion that the development of certain disease states is facilitated under certain conditions of human constitution and apparently retarded by others.

Another recent attempt to appraise human constitution has been made by

Petersen and Leyinson.⁵ In an extremely detailed and interesting investigation these writers sought to learn something of "the individual constitutional reactivity". This work is an attempt to define "human constitution" in terms of biologic reactions rather than in terms of morphologic attributes. In this respect this newer path should lead to a wealth of important data which, supplementing such studies as those carried out by Draper, should result in a more concrete conception of "human constitution."

The study of human constitution, because it concerns itself with the inherent susceptibilities underlying physical disease in man, does not lend itself to animal experimentation. We cannot add one iota to the knowledge of human constitution by investigations with guinea pigs or rabbits, no matter how carefully conducted and controlled. On the other hand, the study of human material has been hampered by a lack of suitable controls. "The weak link in the chain of evidence in human problems appears to be the biologic controls." And it is for this very reason that the study of human constitution, which is so vitally related to our understanding of disease and to effective preventive medicine, has never lent itself to exact scientific investigation.

This bar to a scientific approach is not entirely insurmountable. To a degree, adequate human controls are available. These are identical twins, one of whom serves as a "control animal" for the other. It occurred to us, therefore, that a study of monozygotic twins should afford a means of measuring the relative importance of

the constitutional susceptibility factor to disease and of the environmental influence. To evaluate the inherent constitutional predisposition to disease, we may observe the progress of certain conditions in one of two identical twins and then note whether a similar effect can be observed on the "control animal", the other of the twins.

This report concerns itself, therefore, with a study of identical twins reported in the medical literature, to determine an answer to the question, "If an individual is by constitution a candidate for a specific disease, would he in another trial at life be prone to develop the same disease?" For identical twins, being derived from the same ovum, are really one individual leading two physical existences. Would two such identical individuals, either in the same or different environments, develop identical pathologic processes? The material collected from the literature offers an impressive array of cases in twins in which the same disease attacked both of identical twins simultaneously, but under conditions which would indicate unmistakably the rôle of a latent *constitutional susceptibility*.

REVIEW OF THE DATA

A review of many different disease entities reported to occur in both of identical twins indicates that the simultaneous diseases of twins can be grouped roughly into two categories: first, conditions arising from obvious developmental defects, which are apparent practically from birth in both twins; second, diseases resulting from less obvious defects, which do not become revealed until a later age.

Identical anomalies of homologous twins have been the subject of numerous reports in the literature. Table 1 affords a résumé of obvious developmental defects observed in identical twins. K. Shirley Smith⁶, for example, reports three cases of congenital heart defect in twins. In each instance both twins exhibited a patent ductus arteriosus. Murray's⁷ review of this subject contains the cases of two sets of twins, in which congenital hypertrophic pyloric stenosis occurred doubly in each pair. His study included summaries of many cases of congenital abnormalities in twins including instances of cleft palate, spina bifida, polydactylism, absence of femora, albinism, and a multitude of other developmental defects. Twins, similarly born with multiple fractures of the extremities and ribs, constituting cases of osteogenesis imperfecta, have been reported by Welz and Lieberman.⁸

Some of the congenital abnormalities of twins do not become manifest until the infants are a few months old. Such are the cases of cretinism and infantile myxedema cited by Hanhart⁹ and by Petschacher.¹⁰ Mongolism has been so often observed in homologous twins that Mitchell and Downing¹¹ believe that in no case has it been demonstrated that mongolism can occur in only one of twins which are the result of a single ovum pregnancy.

Abt¹² calls attention to the fact that identical twins show a ready disposition to rickets, which may become apparent when the infants have reached a few months of development. In this connection, too, Atlee and Tyson¹³ have reported the unusually early de-

velopment of tetany, which rarely sets in before four months of age, but which came to his attention in twins eight weeks of age.

Cases of amyotonia congenita (Oppenheim's disease), not apparent at

not become apparent until later, when normal infantile movements are found lacking.

On the whole, this first series of cases demonstrates the fact that homologous twins often develop identical

TABLE I
TABLE SHOWING CASES REPORTED IN THE LITERATURE OF THE SIMULTANEOUS OCCURRENCE OF DEVELOPMENTAL DEFECTS IN IDENTICAL TWINS APPARENT PRACTICALLY FROM BIRTH

Condition	Number of Sets of Twins	Author and Reference
Anatomic defects Congenital heart defects (Patent ductus arteriosus)	3	Smith, K. S.: Arch. Dis. Child., 1929, iv, 330-334.
Congenital hypertrophic pyloric stenosis	1 1	Moore, H. L.: South. Med. Jr., 1924, xvii, 187. Davis, H. H.: Jr. Am. Med. Assoc., 1924, lxxxiii, 686.
Cases of spina bifida, polydactylism, cleft palate, absence of femora, etc.		Murray, G. R.: Lancet, 1925, i, 529.
Osteogenesis imperfecta	1	Welz, W. E., and Lieberman, B. L.: Am. Jr. Obst. and Gynec., 1927, xiv, 49-54.
Cretinism	1	Hanhart, quoted by Siemens, H. W.: Die Zwillingspathologie, J. Springer, Berlin, 1924.
Myxedema	1	Petschacher: Wien. Klin. Wchnschr., 1922, xxxv, 749.
Mongolian idiocy in twins	3	Mitchell, A. G., and Downing, H. F.: Am. Jr. Med. Sci., 1926, clxxii, 866-872.
Disposition to rickets	Many	Abt, I. A.: Jr. Iowa Med. Soc., 1924, xiv, 395.
Tetany	1	Atlee, E. D., and Tyson, R. M.: Arch. Pediat., 1930, xlvii, 513-520.
Amyotonia congenita (Oppenheim's disease)	1	Forbus, W. D., and Wolf, F. S.: Bull. Johns Hopkins Hosp., 1930, xlvii, 309-322.

birth but manifest in both identical twins at the age of five months, have been described by Forbus and Wolf,¹⁴ who indicate that while the original germ defect is present from birth in the anterior horn cells of the spinal cord, the visible manifestations of the disease, such as muscular weakness, do

flaws in their embryonic building material, which become discernible in the growing infants as a dual anomaly or weakness.

The most interesting of the simultaneous abnormalities of identical twins are those which are presented late in life in a synchronous and often

dramatic manner. These may be grouped briefly into four categories, namely.

1. Neoplastic diseases.
2. Nervous and mental diseases,
3. Non-infectious systemic diseases,
4. Infectious diseases.

The simultaneous occurrence of neoplastic diseases in twins has been reported in a number of instances (table 2), and has in most cases been explained as a manifestation of a developmental defect common to both twins. Illustrative cases in this series are such as have been reported, notably by Croom,¹⁵ Benedict,¹⁶ Leavitt,¹⁷ Burkard,¹⁸ and Champlin.¹⁹ From the Mayo Clinic, Benedict has reported twin sisters who both developed retinoblastoma of the left eye, within seven months of each other. Burkard's report concerns twin sisters, both of whom at the age of 21 years developed fibroadenomas not only of the same breast, but of the same part of the breast. The twin brothers observed by Champlin had both developed small round cell sarcomas of the right testicle within a few years of each other. One of these patients died; the other was saved by timely operation because the diagnosis was early suspected.

Since normally the behavior of identical twins is remarkably alike, their similar mental aberrations are not surprising. By far the bulk of reports upon the diseases of monozygotic twins concerns their identical nervous and mental afflictions (table 3).

Soukhanoff²⁰ has reviewed 33 cases in which the form of mental disease was the same in each pair; and in which, frequently, periods of normality occurred in the psychotic twins at

the same time, even though the individual patients were in separate institutions. Likewise, Duncan and Campbell²¹ have written on 29 instances of mental disease in twins showing duplicate cases of dementia praecox, manic-depressive psychosis, paranoia, and so forth, which came on very often at the same time and in the same manner, and in several instances, even though the individual twins lived in different cities.

In the four sets of psychotic twins reported by Smith,²² the twins rather than the single children in a family became psychotic. This writer pointed out the significant fact that three of the four sets of twins had no hereditary psychopathic taint. Frantz²³ describes twin brothers, again without familial psychotic antecedents, who within two years of each other developed dementia praecox. Similar illustrations of homochronous dementia in twins have been furnished by Marie,²⁴ Worcester,²⁵ Wilson and Wolfsohn,²⁶ and others. Wilson and Wolfsohn cite the interesting observation that there is not a single instance in which dementia praecox occurred in only one of identical twins, and they conclude that when nervous disease thus occurs in duplicate, it is most probably the result of inherent defects present in both twins. Other examples of nervous or mental aberrations have been reported by Gill,²⁷ Clouston and Savage,²⁸ Toledo,²⁹ Hess,³⁰ Targowla,³¹ and others.

The systemic diseases, not of infectious origin, occurring simultaneously in homologous twins, comprise a variety of conditions, chief of which is diabetes mellitus (table 4). W. S.

TABLE II
TABLE SHOWING THE OCCURRENCE OF NEOPLASTIC DISEASES IN IDENTICAL TWINS

Condition	Number of Sets of Twins	Sex	Age of Twins at Onset of Symptoms	Remarks	Author and Reference
Adenocarcinoma with myoma of the uterus	1	F	53-53 yrs.	First menstruated on the same day and from 30 years of age suffered from menorrhagia until the menopause at 50.	Croom, quoted by Murray, G. R.: Lancet, 1925, i, 529.
Papilloma of larynx	1				Szontagh, V., quoted by Murray (<i>ibid.</i>)
Retinoblastoma	1	F		Homologous eye of each twin involved within 7 months of each other.	Benedict, W. L.: Arch. Ophth., 1929, ii, 545-548.
Glioma of cerebellum	1			Death at 6½ and 8½ years, respectively.	Leavitt, F. H.: Arch. Neurol. and Psychiat., 1928, xix, 617-622.
Fibroadenoma	1	F	21-21 yrs.	Surprisingly synchronous development of fibroadenomas of same part of left breast.	Burkard, H.: Deutsch. Ztschr. f. Chir., 1922, clxix, 166-174.
Sarcoma of testes	1	M	24-31 yrs.	Right testicle in both involved by small round cell sarcoma. One lived after early discovery and operation.	Champlin, H. W.: Jr. Am. Med. Assoc., 1930, xcvi, 96-97.

TABLE III
TABLE SHOWING CASES REPORTED OF THE SIMULTANEOUS OCCURRENCE OF NERVOUS AND MENTAL DISEASES IN IDENTICAL TWINS

Condition	Number of Sets of Twins	Sex	Age of Twins at Onset of Symptoms	Remarks	Author and Reference
"Insanity"	33			Mostly cases of dementia praecox, paranoia, and manic-depressive psychoses, coming on in twins at about the same time, and in the same manner. Often these lived in different cities.	Soukhanoff, S.: Arch. Med. Psychol., 1900, xii, 8th series, 214. Duncan, and Campbell, D.: Zwillingsirresein u. induziertes irrecsein, Inaug. Diss. Leipzig, 1902.
	29				
"Psychoses" (miscellaneous)	4	F	47-45 yrs. 22-23 yrs. 26 yrs. 43-43 yrs.	The simultaneous onset of psychoses in monozygotic twins is strikingly demonstrated in this series. In one sister no psychosis developed, only a marked religiosity.	Smith, P.: New York Med. Jr., 1912, xvi, 1268-1272.
Dementia praecox	1	M	18-20 yrs.	Developed within two years of each other.	Frantz, M. H.: Jr. Nerv. and Ment. Dis., 1919, I, 325-330.
Dementia	3	F	Menopause	Twins, living apart, developed psychosis same year at menopause. These twins exhibited similar behavior abnormalities although in different parts of institution.	Marie, A.: Encéphale, 1927, xxii, 370-372.
Mania	1	M	26-26 yrs.	Both developed tuberculosis within a month of each other, although one was in the institution two years prior to the other.	Worcester, W. L.: Am. Jr. Insanity, 1890-1891, xlvii, 535-537.

TABLE III—(Continued)

Condition	Number of Sets of Twins	Sex	Age of Twins at Onset of Symptoms	Remarks	Author and Reference
Feeble-mindedness with cerebral diplegia	1	M	Early childhood		Wilson, S. A. K., and Wolfsohn, J. M.: Arch. Neurol. and Psych., 1929, xxi, 477-490.
Congenital nuclear ophthalmoplegia	1	F	Early childhood		
Migraine	1	F		Attacks occurred at same time even if they were at different places. Both became insane at same time.	Gill, C.: Jr. Mental Sci., 1883, xxviii, 540.
Paresis	1	M	37-37 yrs.	Infected at same time; died at same time.	Clouston and Savage: Jr. Mental Sci., 1888, xxxiv, 65.
Epilepsy	1	F	8-8 yrs.	Onset of epilepsy within a few months of each other. Both became insane within two months of each other.	Toledo, R. M.: Jr. Mental Sci., 1919, lxxv, 262.
	1	F	9-13 yrs.		Wilson, S. A. K., and Wolfsohn, J. M.: Arch. Neurol. and Psychiat., 1929, xxi, 477-490.
Friedreich's ataxia	1	M	10-10 yrs.		Hess, J. H.: Med. Clin. of North Am., 1922, v, 1749-1755.
Disseminated sclerosis	1	F		Was present in one sister at early age; re- mained latent in the other until the fif- tieth year.	Targowla, R., La Mache, A., and Daussy, H.: Encéphale, 1927, xxii, 487-489.

Curtis³² summarizes 13 cases of diabetes in twins. In the case reported by von Michaelis,³³ twin brothers, both obese, who followed different occupations, at the age of sixty years simultaneously developed diabetes, later leg paresthesias, perforating ulcers of the toes, and great psychic excitement. These brothers died within a few months of each other of uremia.

Another striking illustration in this series of the occurrence of diabetes in identical twins is that cited from Wolfsohn.²⁶ Twin sisters without familial antecedents of the disease, one of whom lived in San Francisco and the other in New York, simultaneously developed diabetes in their fifty-second year, and died within a short time of each other of cerebral hemorrhage. Other reported instances of the occurrence of diabetes in both of identical twins are those of Kückens,³¹ von Müller,³⁵ Murray,⁷ Twinem,³⁶ Wilder (in a personal communication to Curtis³²) Bunce and Dougherty,³⁷ and Strouse.³⁸

The appearance almost simultaneously of chronic lymphatic leukemia in identical twin brothers has been described by Dameshek, Savitz, and Arbor.³⁹ The brothers, both cobblers, developed symptoms of chronic lymphatic leukemia in their fifty-sixth year and suffered a similar course, and died within sixty-eight days of each other.

Isaac Abt¹² has interestingly presented the fact that he and his twin brother were apparently both victims of cholelithiasis, his twin brother having died of "jaundice" previously.

Among the other medical conditions observed simultaneously in identical

twins have been nephritis,⁴⁰ bronchial asthma,⁴¹ bronchiectasis,⁴² psoriasis,⁴³ cataract,⁴⁴ pituitary anomalies,⁴⁵ Hodgkin's disease,⁴⁶ and Von Jaksch's anemia.^{47,18} In most of these cases the time of onset or the time of attacks was remarkably synchronous in any given set of twins. This tendency was well realized by the brothers reported by Trousseau, one of whom wrote his twin in a distant city: "I am now having my rheumatic ophthalmia, you must be having yours."

The simultaneous affliction of twins by any of the acute infectious diseases, especially the contagious diseases of childhood, are too numerous to mention. Galton¹⁰ and other observers, have noted, moreover, that such simultaneous attacks are most frequent in identical twins, less frequent in heterozygotic twins, and least common in ordinary siblings. Having observed this predisposition to simultaneous development of contagious diseases in no less than 9 out of 35 cases observed, Galton attributed this phenomenon to the like degree of susceptibility and defense mechanism inherited by both twins.

Remarkable instances of bacterial disease acting similarly and simultaneously in both of twin sisters have been described by Kretschmer⁴⁹ (table 5). The father of the twins had suffered with "white swelling of the knee". Within seven months of each other the sisters were admitted to the hospital, neither presenting any signs of active pulmonary tuberculosis, yet both having renal tuberculosis preponderantly in the right side. In both cases extensive calcification of the tuberculous process was found.

TABLE IV
TABLE SHOWING THE SIMULTANEOUS OCCURRENCE OF CERTAIN SYSTEMIC CONDITIONS (NON-INFECTIOUS) IN IDENTICAL TWINS

Condition	Number of Sets of Twins	Sex	Age of Twins at Onset of Symptoms	Remarks	Author and Reference
Diabetes mellitus	1	F	19-67 yrs.		Curtis, W. S.: Jr. Am. Med. Assoc., 1929, xcii, 952-956.
	1	F	3-13 yrs.	Ten years interval between onset of diabetes in one and the other.	
	1	M	10-12 yrs.	Not absolutely identical twins.	
	1	F	17-29 yrs.	No familial antecedents with diabetes. Onset of diabetes 12 years apart.	
	1	M	60-60 yrs.	Also developed simultaneously leg paresis, perforating ulcers, psychic excitement; both died of uremia.	von Michaelis: Arch. f. Rassen- u. Gesellschaftsch.-Biol., 1904, i, 198.
	1	M		Developed diabetes within two months of each other.	Kückens, H.: Klin. Wchnschr., 1925, iv, 2289-2291.
	1	M	advanced age	Both died of same cardiac complication within a few years of each other.	von Müller, Quoted from Siemens, H.: "Die Zwillingspathologie", Berlin, 1904.
	1	F		Diabetes developed the same year, rapid course in both.	Murray, G. R.: Lancet, 1925, i, 529-532.
	1	F	24-31 yrs.		Twinem, F. P.: N. Y. State Jr. Med., 1927, xxvii, 1192.
	1	F	11-11 yrs.	Diabetes developed in one ten weeks after its onset in the other.	Wilder, R. M.: (Personal communication to Curtis).
	1	F	52-52 yrs.	No antecedent family history of diabetes. One lived in New York, other in San Francisco. Both died of cerebral hemorrhage.	Wolfsohn, J. M.: (Personal communication to Curtis).

	1	M	27-27 yrs.	No family history of diabetes. Developed the disease within four months of each other. Blood sugars 500-550.	Bunce, A. H., and Dougherty, M. S.: Jr. Am. Med. Assoc., 1929, xcii, 52.
	1	F-M	11-11 yrs.	Not identical twins.	Strouse, S.: Med. Clin. N. Am., 1918, i, 1241-1243.
Chronic lymphatic leukemia	1	M	56-56 yrs.	Death within 68 days of each other.	Dameshek, W., Savitz, H. A., and Arbor, B.: Jr. Am. Med. Assoc., 1929, xcii, 1348.
Cholelithiasis	1	M		Case of Dr. Abt and twin brother. One had cholelithiasis; brother died of jaundice previously.	Abt, I. A.: Jr. Iowa Med. Soc., 1924, xiv, 395-403.
Nephritis	1	M		Died of Bright's disease within seven months of each other.	Galton, Sir F.: Pop. Sci. Month., 1875, viii, 345-357.
Bronchial asthma (with rheumatic ophthalmia)	1	M		Although in different places developed simultaneous attacks.	Trousseau, quoted by Cockayne, E. A.: Brit. Jr. Child. Dis., 1911, viii, 487-491.
Bronchiectasis	1	F	18-18 yrs.	Similar roentgenographic findings in chest and skull.	von Lossow, O.: Deutsch. Ztschr. f. Chir., 1928, ccxii, 71.
Psoriasis	1	F	12-13 yrs.	No family history of psoriasis.	Lortat-Jacob, Michaux, L., and Sicard, R.: Médecine, 1927, ix, 122-124.
Cataract	1	M		Simultaneous onset at advanced age.	Laycock: British and Foreign Med. Rev., 1844, 169.
Pituitary anomalies	1	M	16 yrs.	Radiographic evidence of abnormally small sella turcica.	Samaja, N.: Chir. degli organ. (Abstracted in Jr. Am. Med. Assoc., 1922, lxxviii, 765.)
Hodgkin's disease	1	M	4-5 yrs.	Developed within 18 months of each other.	Peacocke, G.: Lancet, 1904, ii, 1571.
von Jaksch's anemia	1	F	12 mos.	One died, other recovered. (Presumably identical twins)	Jones, T. D.: Va. Med. Month., 1927, liv, 283-285.
	1	M		Identical pseudoleukemias with similar blood picture, engorged abdominal veins, enlarged spleen and liver. Death about same time.	Dyson, J. E.: Jr. Iowa Med. Soc., 1927, xvii, 321-322.

TABLE V
TABLE SHOWING THE SIMULTANEOUS OCCURRENCE OF INFECTIOUS DISEASES IN IDENTICAL TWINS

Condition	Number of Sets of Twins	Sex	Age of Twins at Onset of Symptoms	Remarks	Author and Reference
Renal tuberculosis	1	F		No active pulmonary tuberculosis. Within 7 months of each other both twins showed signs of bilateral renal tuberculosis, most marked on the right side.	Kretschmer, H. L.: Ann. Surg., 1921, lxxiii, 65-71.
Pulmonary tuberculosis associated with mania	1	M	26-26 yrs.	Both developed tuberculosis within a month of each other; disease ran a rapid course in both.	Worcester, W. L.: Am. Jr. Insanity, 1890-1891, xlvii, 535-537.
Rheumatism	1	F	7 yrs.	Separated at 18 months of age. One lived in London; other in Ontario. Both suffered a good deal from tonsillitis, bronchitis, and rheumatism.	Newman, H. H.: Jr. of Heredity, 1929, xx, 57.
Primary chronic polyarthritis (infectious)	1	M	11-18 yrs.	No familial history of arthritis. Bilateral symmetrical involvement of joints with ankylosis.	Ley, J., and Snoeck, J. J.: Presse méd., 1931, xxxix, 264-268.

The twins reported by Worcester,²⁵ who developed mania simultaneously, likewise both developed pulmonary tuberculosis which ran an equally fulminating course in each.

Another noteworthy instance of simultaneous and similar bacterial activity has been observed by Newman.⁵⁰ Twin sisters were separated at 18 months of age, one residing in London, the other in Ontario. Both had attacks of measles at seven years of age, and subsequently suffered particularly from tonsillitis and bronchitis; both ultimately manifested frank evidence of rheumatic disease.

Primary chronic polyarthritis has been observed simultaneously in identical twin sisters by Ley and Snoeck.⁵¹ The children had no hereditary history of arthritis. However, both, within a few years of each other, developed bilateral, symmetrical involvement of the joints, with ankylosis.

DISCUSSION

The striking occurrence of identical diseases in identical twins, these conditions often developing at about the same time and running so often such a remarkably similar course, has a real bearing on the answer to the questions we have raised. Such occurrence is remarkable but not in the least mysterious. The mechanism behind the simultaneous appearance of disease in twins of advanced age is almost as definite as the mechanism behind the face of a clock, which causes the gong to strike when the hands arrive at the given hour. Let us examine this mechanism, the constitutional factor.

The development of identical disease, in each of two physically distinct

individuals derived from a single ovum, points unmistakably to some common denominator. This factor we choose to call the factor of susceptibility. It really represents a defect in the constitutional structure in each of the two individuals.

When this defect is patent at birth, it may be apparent as a duplicate error of gross morphologic nature. Such, for example, are the cases of congenital heart defects, spina bifida, or cleft palate.

In certain instances the inherent anatomic defect may be less obvious at the start, the abnormality not becoming apparent until a later age. Such, for example, is the case where each of twins is born with under-development of the anterior horn cells of the spinal cord. Since skeletal muscle development depends upon the trophic influence of these motor cells, this development fails, and as a result it becomes apparent at the third or fifth month that the child cannot raise its head well, cannot nurse satisfactorily, cannot move its limbs well, and in brief shows all the features of a case of amyotonia congenita or Oppenheim's disease. What we see is a muscular maldevelopment; what is hidden is the causal weakness in the motor cells of the spinal cord.

While the importance of a constitutional defect in the production of certain congenital anatomic abnormalities is obvious, it is still not often realized that the development of such conditions as diabetes, or nephritis, cholelithiasis, or renal tuberculosis, and probably all disease, is influenced by the constitutional predisposition or resistance to such disease. How can one escape

the conclusion that such an inexorable constitutional influence is at work in the production of identical types of neoplastic disease in identical twins? Such cellular activity must be the result of a ripening process in a hidden pathologic defect which had remained latent for a variable period of years. That such identical tumors may not come to fruition until the fifth decade indicates that a constitutional basis for disease which does not become apparent until late in life must still be sought. If it is assumed that some sort of inherent defect susceptible to neoplastic change is inborn, then it would appear that some adequate environmental stimulus is necessary to determine the ultimate development of the neoplasm.

Functional failures have likewise their counterpart in the category of disease. Under certain conditions of living, for example, a latent functional defect of the islands of Langerhans will become manifest at some later time as frank diabetes, as in the twins here reported. Likewise, an obscure defect of mental function will ultimately spell psychosis in individuals so constituted. The probabilities are, however, that the mental derangement will not occur until the individual either arrives at one of the critical developmental periods, such as puberty or the menopause, or experiences some unusual environmental stress.

Considering the many cases of mental disease, of diabetes, of blood dyscrasias, renal tuberculosis, cholelithiasis, bronchial asthma, arthritis, and so on, observed in identical twins and reviewed in our series, one cannot escape the conclusion that in such twins

the constitutional basis for the development of disease is a tangible factor. The frequent development of identical disease in identical twins at the same period of life, and particularly at different periods of life, indicates beyond the possibility of doubt that the latent predisposition to a given disease lay in wait for these individuals, and depended only upon an adequate environmental stress to become apparent. Clearly depicting such a possibility is the case of twins reported by Kretschmer,⁴⁹ both of whom, within seven months of each other, developed renal tuberculosis, preponderantly in the right kidney. The inherent weakness in this instance was evidently in the right kidney. Disease did not result, however, until this weakened structure in each of the two twins met with the invasive organism. The lungs, and other sites equally open to the attack of the organism were significantly capable of escape. Incidentally, to guess whether such susceptibility is specific for any particular noxa is far beyond present knowledge.

So far it is compellingly demonstrated that in individuals for whom a very specific biologic control exists, that is, in identical twins, the rôle of pathologic susceptibility is a large factor. Through a study of the history of these twins the disease process is seen to be the result of some element in the environment plus the necessary vulnerable spot in the individual. So regarded, disease is seen to be not a capricious event but a necessary sequence that must follow when an individual harboring a definite inborn error is placed in an environment containing many possible

noxious elements. To most of the disease dangers which beset us we are probably not susceptible, else we were all in a bad way, but we all have the equivalent of an Achilles' heel.

of the pathologic process with some inherent weakness. The difficulty lies, of course, in the fact that in any given case one has no control experiment such as nature provides in identical twins.

The question may be raised as to how often identical twins do not present during their lives identical disease processes. Whatever the entire answer may be, this much is certain: that only one of the two twins harboring identical disease potentialities may be subjected to environmental stress of a degree sufficient to bring the disease to fruition. In such cases only one of the two twins may develop outspoken disease; the other will remain outwardly free of its manifestations. Such a process is admirably illustrated in one case reported by Smith,²² where one sister became distinctly psychotic in her forty-third year; her twin showed only a marked religiosity, but no definite psychosis. This religiosity was obviously the expression of a trend to mental aberration. The inference is naturally that there existed here some variation either in the degree of susceptibility or in the degree of environmental stress. That susceptibility to some sort of mental disease existed in both of these twins is, however, clearly evident.

Even in one of diabetic twins, the constitutional factor would hardly be impressive, were it not forcibly demonstrated by the simultaneous appearance of the same disease in the other twin.

If we are justified in the inference that the same causative factors are operative in the production of disease in ordinary individuals as in identical twins, then we may conclude that constitutional predisposition to disease is equally paramount. This predisposition is only more strikingly revealed in twins, because in them it is more readily discernible through their biologic controls.

While recent developments in our knowledge of the causes of disease have focused our attention largely on the external factors, it would seem from our study that this focus has produced some distortion. Too great a rôle has been assigned to the purely external causes of disease, too little to the vital intrinsic mechanism. Had nature provided a biologic control, an identical twin, in every instance of human disease, we should long since have been impressed by the predominant rôle of human constitution.

Probably the most significant aspect of our study is in relation to the problem of disease in general, rather than to the problem of disease in twins alone. In any individual case of diabetes, or tuberculosis, or leukemia, it is naturally quite difficult to perceive the constitutional basis. Often the condition does not develop until late in life and this fact has made it even more difficult to link the development

The concept of human constitution has in the past lacked clarity because it lacked definition. The numerous exceptions to the expected disease potentialities associated with the so-called "phthisic habitus", for example, has detracted from the value of this con-

cept in its practical application to the study of disease. This is not surprising because "habitus" represents only the superficial pattern in the fabric. It is really the warp and woof of that fabric that is the basis of human constitution.

We are only now beginning to study these intimate components of the human fabric. The painstaking studies of Draper and of his associates have already revealed myriads of threads that can now be followed to the individual's disease potentialities. Thus, by detailed anthropometric and psychologic investigations on clinical material comprising a variety of disease entities, they are already able to correlate, to an extent, certain distinct constitutional potentialities with certain definite diseases. The work of Petersen and Levinson enlarged upon the possible indices of human potentiality, by "seeking to define constitution in terms of measurable biologic reactions, rather than in developmental attributes". Their approach is through a study of various physiologic responses of the individual, such as to heat, epinephrine, thyroxin, the effects of manual labor, and other stimuli too numerous even to mention. Just as Draper's data through one mode of approach, so the correlation of these physiologic responses, too, affords a means of appraising various types of

human constitution. We have only begun to unearth the various indices of human constitution. It is to be hoped that the impetus gained from such investigations will in time result in studies that will corral all of the factors comprising the various types of individual make-up. When this has been achieved it is likely that the adequate clinical investigation of a patient's disease will be preceded by the analysis of the individual himself.

SUMMARY AND CONCLUSION

The study of pathologic conditions in identical twins affords an excellent means of discovering disease potentialities.

The element of constitutional predisposition is most clearly evident in identical twins, since one of these individuals serves as a control for the other.

It is suggested that by such controlled investigation and by other related biologic means, including explorations into the chemical and serologic reactions of the individual, the isolation of the specific components of disease susceptibility is made possible. When the clinician is in possession of these objective indices of various types of human constitutions, he will then be in a position to study thoroughly the patient as well as his disease.

BIBLIOGRAPHY

¹MÜLLER, VON FRIEDRICH: *Konstitution und Individualität*, Rektorat — Antrittsrede gehalten an der Universität München, 1920, J. Lindawersche Universitäts-Buchhandlung, München.

²BAUER, J.: *Die konstitutionelle Disposition zu inneren Krankheiten*, 1921, Berlin.

³BORCHARDT, L.: *Klinische Konstitutionslehre*, 2 Ed., 1930, Berlin.

⁴DRAPER, G.: *Human constitution, a consideration of its relationship to disease*, 1924, W. B. Saunders Company, Philadelphia.

⁵PETERSEN, W. F., and LEVINSON, S. A.: *The skin reactions, blood chemistry and*

- physical status of "normal" men and of clinical patients, *Arch. Path.*, 1930, ix, 151-444.
- ⁶SMITH, K. S.: Congenital cardiac disease in identical twins, *Arch. Dis. Childhood*, 1929, iv, 330-334.
- ⁷MURRAY, G. R.: Twins in health and disease, *Lancet*, 1925, i, 529.
- ⁸WELZ, W. E., and LIEBERMAN, B. L.: Report of case of osteogenesis imperfecta in twins, *Am. Jr. Obst. and Gynec.*, 1927, xiv, 49-54.
- ⁹HANHART, quoted by SIEMENS, H. W.: Die Zwillingspathologie, ihre Bedeutung, ihre Methodik, ihre bisherigen Ergebnisse, 1924, J. Springer, Berlin.
- ¹⁰PETSCHACHER, quoted by MURRAY, G. R.: Twins in health and disease, *Lancet*, 1925, i, 529.
- ¹¹MITCHELL, A. G., and DOWNING, H. F.: Mongolian idiocy in twins, *Am. Jr. Med. Sci.*, 1926, clxxii, 866-872.
- ¹²ART, I. A.: Diseases and fate of twins, *Jr. Iowa State Med. Soc.*, 1924, xiv, 395-403.
- ¹³ATLEE, E. D., and TYSON, R. M.: Tetany occurring in identical twins at eight weeks of age, *Arch. Pediat.*, 1930, xlvii, 513-520.
- ¹⁴FORBUS, W. D., and WOLF, F. S.: Amyotonia congenita (Oppenheim's disease) in identical twins, *Bull. Johns Hopkins Hosp.*, 1930, xlvii, 309-322.
- ¹⁵CROOM, quoted by MURRAY, G. R.: Twins in health and disease, *Lancet*, 1925, i, 529.
- ¹⁶BENEDICT, W. L.: Retinoblastoma in homologous eyes of identical twins, *Arch. Ophth.*, 1929, ii, 545-548.
- ¹⁷LEAVITT, F. H.: Cerebellar tumors occurring in identical twins, *Arch. Neurol. and Psychiat.*, 1928, xix, 617-622.
- ¹⁸BURKARD, H.: Gleichzeitige und gleichartige Geschwulstbildung in der linken Brustdrüse bei Zwillingsgeschwestern. Zugleich ein Beitrag zur Cohnheimschen Theorie der fötalen Geschwulstanlage, *Deutsch. Ztschr. f. Chir.*, 1922, clxix, 166-174.
- ¹⁹CHAMPLIN, H. W.: Similar tumors of testis occurring in identical twins, *Jr. Am. Med. Assoc.*, 1930, xcv, 96-97.
- ²⁰SOUKHANOFF, quoted by MURRAY, G. R.: Twins in health and disease, *Lancet*, 1925, i, 529.
- ²¹DUNCAN, and CAMPBELL, D.: Zwillingsirresein u. induziertes irresein, *Inaug. Diss.*, 1902, Leipzig.
- ²²SMITH, P.: Psychoses occurring in twins, *N. Y. Med. Jr.*, 1912, xcvi, 1268-1272.
- ²³FRANTZ, M. H.: Dementia praecox in twins, *Jr. Nerv. and Ment. Dis.*, 1919, l, 325-330.
- ²⁴MARIE, A.: Six cas de démence homochrone chez des soeurs et des jumelles, *Encéphale*, 1927, xxii, 370-372.
- ²⁵WORCESTER, W. L.: Insanity in twins, *Am. Jr. Insanity*, 1890-1891, xlvii, 535-537.
- ²⁶WILSON, S. A. K., and WOLFSOHN, J. M.: Organic nervous disease in identical twins, *Arch. Neur. and Psychiat.*, 1929, xxi, 477-490.
- ²⁷GILL, C., quoted by MURRAY, G. R.: A study of twins in health and disease, *Lancet*, 1925, i, 529-532.
- ²⁸CLOUSTON and SAVAGE, quoted by WILSON, S. A. K., and WOLFSOHN, J. M.: Organic nervous disease in identical twins, *Arch. Neur. and Psychiat.*, 1929, xxi, 477-490.
- ²⁹TOLEDO, R. M.: Notes on two cases of epilepsy in twins, with photographs, *Jr. Mental Sci.*, 1919, lxxv, 262.
- ³⁰HESS, J. H.: Friedreich's ataxia in twin boys, showing progressive changes in their nervous systems referable to spinal cord, cerebellum, and probably cerebrum following an attack of influenza in 1918, *Med. Clin. N. Am.*, 1922, v, 1749-1755.
- ³¹TARGOWLA, R., LA MACHE, A., and DAUS-SY, H.: Débilité mentale, troubles du caractère et débilité motrice chez deux soeurs jumelles. Atteinte disséminée frieste du névraxe, *Encéphale*, 1927, xxii, 487-489.
- ³²CURTIS, W. S.: Diabetes in twins, *Jr. Am. Med. Assoc.*, 1929, xcii, 952-956.
- ³³VON MICHAELIS, R.: Die erbliche Beanlagung bei der menschlichen Tuberkulose nach eigenen Beobachtungen, *Arch. f. Rassen- u. Gesellsch.-Biol.*, 1904, i, 198-209.
- ³⁴KÜCKENS, H.: Über Heredofamiliarität bei Paralysis agitans. Zugleich ein Beitrag zum hereditär bedingten Auftreten

- des Diabetes mellitus bei eineiigen Zwillingen, *Klin. Wchnschr.*, 1925, iv, 2289-2291.
- ³⁵VON MÜLLER, quoted from SIEMENS, H. W.: *Die Zwillingspathologie, ihre Bedeutung, ihre Methodik, ihre bisherigen Ergebnisse*, 1904, J. Springer, Berlin.
- ³⁶TWINEM, F. P.: Identical twins and problem of heredity, *N. Y. State Jr. Med.*, 1927, xxvii, 1192-1193.
- ³⁷BUNCE, A. H., and DOUGHERTY, M. S.: Diabetes mellitus in twins, *Jr. Am. Med. Assoc.*, 1929, xcii, 52-53.
- ³⁸STROUSE, S.: Juvenile diabetes in twins, *Med. Clin. N. Am.*, 1918, i, 1241-1243.
- ³⁹DAMESHEK, W., SAVITZ, H. A., and ARBOR, B.: Chronic lymphatic leukemia in twin brothers aged 56, *Jr. Am. Med. Assoc.*, 1929, xcii, 1348-1349.
- ⁴⁰GALTON, F.: The history of twins, as a criterion of the relative powers of nature and nurture, *Pop. Sci. Month.*, 1875, viii, 345-357.
- ⁴¹TROUSSEAU, quoted by COCKAYNE, E. A.: Disease in homogenous twins, *Brit. Jr. Child. Dis.*, 1911, viii, 487-491.
- ⁴²VON LOSSOW, O.: Angeborene Bronchektasenbildung bei Geschwistern und einiigen Zwillingen, *Deutsch. Ztschr. f. Chir.*, 1928, ccxii, 71-80.
- ⁴³LORTAT-JACOB, L., MICHAUX, L., and SICARD, R.: Psoriasis gémellaire, *Médecine*, 1927, ix, 122-124.
- ⁴⁴LAYCOCK, quoted by MURRAY, G. R.: Twins in health and disease, *Lancet*, 1925, i, 529-532.
- ⁴⁵SAMAJA, N.: Radiographic study of twins with pituitary anomalies, *Chir. degli organ.* (Abstr., *Jr. Am. Med. Assoc.*, 1922, lxxviii, 765).
- ⁴⁶PEACOCKE, G.: Hodgkin's disease, *Lancet*, 1904, ii, 1571.
- ⁴⁷JONES, T. D.: von Jaksch's disease and secondary anemia occurring in twins, with report of cases, *Va. Med. Month.*, 1927, liv, 283-285.
- ⁴⁸DYSON, J. E.: Case report (infantile pseudoleukemia in twins), *Jr. Iowa Med. Soc.*, 1927, xvii, 321-322.
- ⁴⁹KRETSCHMER, H. L.: Renal tuberculosis in twins, *Ann. Surg.*, 1921, lxxiii, 65-71.
- ⁵⁰NEWMAN, H. H.: Mental and physical traits of identical twins reared apart, *Jr. Hered.*, 1929, xx, 49-64.
- ⁵¹LEY, J., and SNOECK, J. J.: Polyarthrite symétrique primitive à évolution chronique, progressive et destructive chez des soeurs jumelles, *Presse méd.*, 1931, xxxix, 264-268.

Editorials

SPONTANEOUS HYPOGLYCEMIA VERSUS HYPERINSULINISM

The symptoms associated with an abnormally low blood sugar have become relatively well known to the medical profession in recent years. The advent of insulin brought into prominence the clinical manifestations of insulin overdosage, the so-called insulin shock, and but a few years elapsed before Harris in 1924 drew attention to the spontaneous occurrence of similar attacks which he showed to be accompanied by low blood sugar levels. Such instances of spontaneous hypoglycemia, that is hypoglycemia unassociated with the administration of insulin, have been reported with increasing frequency in the medical literature.

In the milder types of reaction the symptoms consist of weakness, tremor, sweating and sensations of coldness and numbness of the extremities. There may be a feeling of intense hunger, though this is by no means constant. In more severe attacks diplopia and tinnitus may be complained of, and emotionalism, mental confusion and even mania may be observed. Finally, stupor, or deep unconsciousness may develop with or without epileptiform convulsions. The blood sugar in milder cases may not be much below 70 milligrams in 100 cubic centimeters of blood, but in the more severe type of hypoglycemic reaction it is usually less

than 50 milligrams and sometimes less than 30.

It seems well established that the development of these striking symptoms is dependent in some way upon the low blood sugar level since in the majority of cases prompt relief is obtained by the oral or intravenous administration of glucose. In symptomatology, in the presence of a low blood sugar level, and in the relief afforded by the giving of glucose, these cases of spontaneous hypoglycemia parallel the cases of insulin shock. It is natural, therefore, that the condition is frequently called hyperinsulinism.

The use of this term is certainly justified in any case like that described by Wilder, Allan, Power, and Robertson.¹ Their patient at times required 1000 grams a day of glucose to keep the blood sugar above hypoglycemic levels. Operation and later autopsy showed the presence of a carcinoma of the pancreas, originating from islet cells, with metastatic growth in the liver. From these metastases, a large yield of insulin was obtained. This case, however, still stands alone in the completeness of proof of the existence of hyperinsulinism. Almost as convincing are the cases reported by How-

¹WILDER, R. M., ALLAN, F. N., POWER, M. H., and ROBERTSON, H. E.: Carcinoma of the islands of the pancreas; hyperinsulinism and hypoglycemia, Jr. Am. Med. Assoc., 1927, lxxxix, 348-355.

land, Campbell, Maltby and Robinson,² by Carr, Parker, Grove, and Fisher,³ and by Womack, Gnagi, and Graham.⁴ In these cases relatively small adenomas of the pancreas made up of islet cells were removed surgically with resultant cure of severe forms of hypoglycemic attacks. The demonstration of the insulin content of these tumors is lacking, however, and Bensley, who carefully studied the histology of these tumors, found certain cytological features which were not typical of normal islet cells. But even conceding their insulin content as highly probable, the small size of one tumor (0.5 cm. in diameter), in comparison with the normal islet content of the pancreas, seems to necessitate the conception that such tumors can produce hypoglycemia only through an unregulated secretion of insulin at a time when the blood sugar level is low. So that perhaps the symptoms in these patients were due, not so much to hyperinsulinism in a quantitative sense, as to insulin delivered in an unphysiological manner. The terms *dysinsulinism* and *dysinsulinosis* have been proposed to designate such defects in insulin secretion.

But if there is reason for qualifying the use of the term *hyperinsulinism* in

connection with these cases which possess a definite pathological lesion suggestive of its presence, how much more is caution desirable in the far larger group of cases of idiopathic hypoglycemia to which some authors would apply this term.

The chief factors influencing the blood sugar level are summarized by Cori⁵ as follows:

"The blood sugar level depends on the relative rate at which sugar enters and leaves the blood stream. Maintenance of a constant blood sugar concentration requires an in- and out-flow of sugar of equal magnitude. When this equilibrium is disturbed, the blood sugar may either rise or fall, depending on the preponderance of the processes which contribute or which cause a withdrawal of sugar from the blood. Since the blood sugar of mammals remains normally in the neighborhood of 0.1 per cent, there must exist a regulatory mechanism which is set in motion whenever the blood sugar ranges much below or above this figure. It is now generally accepted that a rise in blood sugar elicits a secretion of insulin and that a fall in blood sugar below a certain level is followed by a discharge of epinephrine. The mechanism of blood sugar regulation is therefore intimately connected with the action of these two hormones on blood sugar production and utilization. Two processes contribute sugar to the blood, namely, absorption of carbohydrate from the alimentary canal and sugar formation in the liver (from glycogen and other sources). The disappearance of blood sugar depends on its oxidation in the

²HOWLAND, G., CAMPBELL, W. R., MALTBY, E. J., and ROBINSON, W. L.: Dysinsulinism: convulsions and coma due to islet cell tumor of the pancreas with operation and cure, Jr. Am. Med. Assoc., 1929, xciii, 674-679.

³CARR, A. D., PARKER, R., GROVE, E., and FISHER, A. O.: Hyperinsulinism from B-cell adenoma of the pancreas. Jr. Am. Med. Assoc., 1931, xcvi, 1363-1367.

⁴WOMACK, N. A., GNAGI, W. B., JR., and GRAHAM, E. A.: Adenoma of the islands of Langerhans with hypoglycemia, Jr. Am. Med. Assoc., 1931, xcvi, 831-836.

⁵CORI, C. F.: Mammalian carbohydrate metabolism. *Physiol. Rev.* 1931, xi, 150

tissues and on its conversion into glycogen and fat; under certain conditions sugar is lost from the blood on account of excretion in the urine."

It is obvious that the possible causes of hypoglycemia are very numerous, and that hyperinsulinism is only one of these. Aside from a quantitative increase in the amount of insulin formed, there may occur a state in which insulin is secreted continuously or at moments of low instead of high blood sugar. Some have supposed that the secretion of an abnormal type of insulin may explain spontaneous hypoglycemia. It is possible that at times normal amounts of insulin may exert an abnormally great effect because of the absence of some opposing substance. Sugar is known to diffuse from the blood at varying rates. The rate of diffusion of sugar through membranes is affected by the presence of very minute amounts of insulin in the solution. It is possible that factors abnormally accelerating diffusion into the tissues may be at fault in some instances of hypoglycemia. Hepatectomy in animals and extensive liver damage in humans are accompanied by hypoglycemia presumably due to an absence of liver glycogen as a source of blood sugar. Defective liver glycogenesis or defective glycogenolysis may equally then be causes of hypoglycemia. Adrenalin normally causes glycogenolysis, and it is understandable, therefore, that disturbances in adrenalin formation or in its timely secretion may allow the blood sugar to fall to hypoglycemic levels. The relationship of the pituitary to the normal blood sugar is far from clear, but since pituitrin will raise the blood sugar in hypoglycemic patients

one must envisage the possibility that there may occur a type of hypoglycemia due to pituitary disease.

It would be needlessly tiresome to discuss theoretical possibilities if in fact all human cases of hypoglycemia exhibited identical clinical physiognomies and if all whose pancreases had been explored surgically had yielded evidence of lesions capable of producing insulin. Such, however, is far from being the case. The hypoglycemic symptoms in the reported cases of hypoglycemia, while on the whole qualitatively similar, have shown the widest variability in their relationship to such factors as exercise, nervous strain, the intake of food, infections, etc. They vary likewise in severity of symptoms, and in tendency to progress or regress. They differ in the type of response they give to the glucose tolerance test and in the benefit they obtain from the use of high carbohydrate diets or of ketogenic diets. They do not exhibit the same effects from the therapeutic administration of glucose or adrenalin or pituitrin. Moreover the great variety of clinical conditions in which an associated hypoglycemia has been observed is evidence in favor of its production by varied mechanisms. Without mentioning all of these clinical associations it may be stated that hypoglycemia has been reported in connection with hypothyroidism. Addison's disease, adenoma of the adrenal, diabetes, acromegaly, pluriglandular syndromes, scleroderma, fatty livers, eclampsia, after serious burns, and in 36 per cent of a group of 33 moribund patients.

It may well be that closer clinical study of patients who exhibit hypoglycemia and the symptoms that accom-

pany it will enable us to determine more definitely which cases are due to pancreatic tumors of islet tissue. The present evidence would seem to indicate that true hyperinsulinism due to such a tumor is among the rarest causes of hypoglycemia. Exploratory operation may well be reserved for those cases in which the severity of the attacks leads to serious disability or is threatening to life. In the absence of a tumor it would seem on theoretical grounds a dubious procedure to resect a large portion of the pancreas as has been proposed, since in such cases there is at present no way of knowing whether the pancreas has been the cause of the symptoms. It is true that the loss of the major portion of the islets could at the worst be compensated for by insulin injections, but the loss of a great deal of the external secretion of the pancreas may prove to have serious consequences. Reported operations of this type have not yielded satisfactory results. For the present it would seem more in accordance with our actual lack of knowledge to designate all cases of hypoglycemia in which no definite proof of cause exists as spontaneous or idiopathic hypoglycemia rather than as cases of hyperinsulinism.

BEDSIDE TEACHING

There is nothing new under the sun. Hippocrates taught at the bedside; and from the later school at Salerno, there has survived the plaint of a patient at what he had to endure from the cold hands of examining students. Today, bedside teaching is no longer the novelty in this country that it was thirty

years ago, when its inclusion in the curriculum was mentioned with conscious pride in the school catalogue. Yet, it is questionable whether in all these centuries the technic of bedside teaching has been improved or has deteriorated.

Too often today bedside teaching consists of the presentation of the history of a patient by the Clinical Clerk and of a fifty minute lecture at the bedside by the Instructor, who may or may not devote a few minutes of this time to the examination of the patient. The lecture is apt to deal with the metabolic abnormalities, the defective hematopoiesis, or the renal functional pathology of the patient, as with anything that can be seen, felt, heard, or smelled, about his body. It is not that this kind of instruction is not of value, but that to give it at the bedside seems unnecessarily hard on the students' feet.

The *raison d'être* for bedside teaching, is demonstration of the patient. There are many ways, of course, of demonstrating. Physical signs may be taught as a part of the elementary course in physical diagnosis and a comparative study of such signs made on different patients in the ward. For example, an interesting period may be spent in analyzing the various types of respiratory difficulties when there is occasion to observe them in a number of different patients; or students may be shown how to differentiate the commoner small red spots on the patient's skin. Such bedside teaching is usually only possible for the physician who is responsible for the ward and hence knows all of its patients intimately.

Quite another type of demonstration

Dr. D. E. Markson (Fellow), Chicago, Ill.—1 reprint;

Dr. James R. Nakada (Associate), St. Louis, Mo.—4 reprints.

Dr. Emil Weiss (Associate), Chicago, Ill., recently resigned, due to ill health, as Professor of Bacteriology at Loyola University School of Medicine.

Dr. Llewellyn Sale (Associate), St. Louis, Mo., was elected President of the Missouri Social Hygiene Association on January 9.

Dr. Leon T. LeWald (Fellow), New York City, has been elected President of the Medical Association of the Greater City of New York.

Dr. George Morris Piersol (Fellow and President), Philadelphia, Pa., was elected President of the Medical Club of Philadelphia at its annual meeting during January.

The Department of Postgraduate Medicine of the University of Michigan and the Michigan State Medical Society offered a postgraduate course in Pulmonary Tuberculosis, March 20-24, 1933, at the University Hospital, Ann Arbor. Dr. Carl V. Weller (Fellow) gave a paper and demonstration on "Pathology of Tuberculosis"; Dr. Arthur C. Curtis (Fellow) gave a lecture on "Value of the Physical Examination in Various Types of Pulmonary Tuberculo-

sis"; and Dr. Salvatore Lojacano (Fellow) gave a lecture on "Treatment—Fundamentals."

Dr. Francis B. Johnson (Fellow), Charleston, S.C., was elected President of the Tri-State Medical Association of the Carolinas and Virginia at its Annual Session at Greenville, S.C., during February.

Dr. Peter Whitman Rowland (Fellow), University, Miss., was elected President-Elect of the Mid-South Postgraduate Medical Assembly at its Annual Meeting in Memphis, February 16. Dr. Arthur F. Cooper (Fellow), Memphis, Tenn., was re-elected Secretary.

Dr. Frederick L. Fenno (Fellow), New Orleans, La., was recently appointed Consulting Neurologist to the Eye, Ear, Nose and Throat Hospital of that City.

Dr. Aldo Castellani (Fellow), New Orleans, La., was recently appointed Director-in-Chief of the Ross Institute and Hospital, London, to succeed the late Sir Ronald Ross.

Dr. J. O. Elrod (Fellow), Forsyth, Ga., has been elected Vice-President of the Monroe County Medical Society for 1933.

Dr. E. C. Swift (Fellow), Jacksonville, Fla., was recently elected Treasurer of the Duval County (Florida) Medical Society.

OBITUARIES

DR. HENRY G. MEHRTENS

Dr. Henry Mehrtens' death came as a sudden shock to his friends and associates. Stricken on February 13 with coronary occlusion, he did well for a few days, but after a second attack he failed rapidly and died on February 28.

Dr. Mehrtens was born and reared in San Francisco and in 1911 he grad-

uated from the University of California. It was to Stanford, however, that he went for his medical work. Somewhat more mature than the average student, he soon displayed unusual ability not only in his specialty of Neuro-Psychiatry but in administrative medicine; it fell to his lot in various times of emergency to serve as Superintendent of Stanford Hospital, and since Dr. William Ophüls' resignation

last fall he acted as Dean of the Stanford Medical School.

Always a student and bibliophile, and a voracious reader of good literature both medical and non-medical, he had a happy faculty of clear speech and sound exposition which at the bedside or in colloquium sustained the interest of his students. Irrepressible scientific curiosity impelled him and his associates to carry out numerous scientific investigations which have made his name familiar to all neuro-psychiatrists. With his patients he had a unique approach: he rode no psychiatric hobby, adhered to no cult and sustained no exclusive thesis. But with a broad technical training and sound psychological background, tempered with unfailing patience and good humor, he led his patients out of the labyrinth of their difficulties and retained them as lifelong friends. Finally, there should be set down as his major contribution the organization along modern lines of the Psychiatric Wards at Stanford Hospital. Dr. Mehrtens had been a Fellow of the American College of Physicians since 1931.

(Furnished by ARTHUR L. BLOOMFIELD, M.D., F.A.C.P., San Francisco, Calif.)

DR. CHARLES HOWARD
MILLER

Dr. Charles Howard Miller, a Fellow of the American College of Physicians

since 1925, died suddenly from coronary occlusion on February 2, 1933, at the Southern Pacific Hospital in San Francisco.

Dr. Miller was sixty-one years of age, a native of Pennsylvania and resident in California since 1880. He was a graduate of Cooper Medical College, now Stanford University Medical School, in 1896. Except for a period of two years in San Juan, Dr. Miller's entire professional life was spent in San Leandro, where he succeeded to the practice of his father on the death of the latter. Beginning thus as a country doctor in what was then a village some miles from Oakland, but now essentially a contiguous part of the larger city, Dr. Miller became one of the most prominent and probably the best beloved of the citizens of his community, which he served in many civic capacities in addition to his busy professional activities.

As a physician, Dr. Miller always exemplified in highest degree the finest traits which, we like to believe, characterize our profession. He was a member of the Alameda County Medical Association and of the American Medical Association and on the staff of the East Oakland Hospital and of the Highland Hospital.

(Furnished by THOMAS C. McCLEAVE, M.D., F.A.C.P., Oakland, Calif.)

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President's Address*

By F. M. POTTENGER, M.D., F.A.C.P., *Monrovia, California*

ONE of the greatest honors which can come to an internist in America is to have his colleagues entrust to his care and guidance the destinies of The American College of Physicians, for this organization stands for the highest ideals and the noblest sentiments which actuate medical men in the pursuit of knowledge and in the application of medical facts to the prevention and cure of disease, and to the alleviation of suffering. A year ago, on assuming the duties of President, I thanked you warmly for the confidence which you reposed in me, and tonight, I again wish to express my grateful appreciation for this high honor.

In accepting the honor, the President also assumes the responsibility of furthering the interests of the organization by keeping in touch with the members and studying their problems. In his Presidential Address he is expected to comment on the subjects which he considers of special importance to the College, either in conducting its inter-

nal affairs, or in advancing and upholding its standards in laboratory and clinical practice; or upon special problems which may confront the College at the time, or press for solution in the near future.

The internal affairs of the College seem to be in good order. Its position in American Medicine is unquestioned. It numbers among its members men who are representative of the best in research, teaching and practice. By the intimate association of its members medical knowledge is furthered, the enthusiasm of the members is increased, and friendships are cemented. While there are many fields in which our organization may direct its energies in the service of Medicine, it has seemed wise thus far to confine our efforts to strengthening our own organization. Heretofore our members have preferred to have the College stand for leadership in medical thought rather than in organization, yet questions of a vital economic nature are arising today both in Medicine and in the body politic which are forcing themselves upon us and calling for leadership in their solution. Would it

*Read at the Seventeenth Annual Clinical Session of the American College of Physicians, Montreal, Canada, February 6-10, 1933.

not be well for the members of the College to answer this call and give to the solution of these problems the aid of their well trained minds?

THE OPEN MIND

From the time of Hippocrates, interest in the study of Medicine has been stimulated by the fact that it has been a continuous excursion into the unknown. New fields to be investigated have required new methods of procedure and taxed the ingenuity of the curious. New facts obtained have called for imagination and patient observation to determine the manner in which they were to be utilized to improve conceptions already held.

One of the difficulties met in the development of Medicine is that which attends advancement in any unfolding science, that of putting a true value both on the ideas already held, and on the new ones which are advanced from time to time.

The medical mind can never become static. It is necessary only to look back a few decades, to see that ideas which were accepted as guiding principles, now, as a result of further investigation, are either greatly modified or wholly displaced. We have many facts which are safely grounded; and many more which, though accepted, are not fully proved.

The open mind in science is the only safe mind, the only mind that can be expected to progress and utilize knowledge as it is acquired. It is the mind which, knowing its limitations, receives new things sympathetically, critically, but with a readiness to displace prevailing belief, no matter how well it seems to be founded, by any new knowledge that may be definitely

proved. Thus, Medicine calls for an openness of mind and a criticalness of judgment such as it is almost impossible to attain. It demands a conservatism born of knowledge and experience, combined with the liberality of the adventurer who considers the known as never final, but always subject to change with increased experience.

Edison is credited with having approached new theories with a rare open-mindedness and to have classified them into two categories: one, that which agreed with what he believed to be true; the other, that which did not agree and so was to be investigated. It requires a well organized and controlled mind to classify data as agreeing or disagreeing with "what one *holds to be true or false*" rather than with "what one *knows to be true or false*." Such a man might never be able to speak with the dogmatism of authority, yet he would be a safe leader to follow, for knowledge to him would be an open book with every page unfinished.

Medical progress has come through continuous questioning. A leader who progresses along accepted lines and pushes the outposts of knowledge a little further than those previously established, but does not depart too much from the known, is readily followed by his confreres; but the leader who climbs over the sides of the groove which confines prevailing thought and constructs a bridge into the unknown, is followed by few. He at once meets opposition from those who are satisfied with their own beliefs and whose minds can not or will not follow.

There is a general belief that the human mind hungers for knowledge,

but it also must be apparent that it often shows a strong tendency to resist the knowledge which would satisfy the hunger; for, as has been so aptly said, "As a means of retarding the entry of unusual notions the human cranium is a well-nigh perfect mechanism." This was well illustrated in the slowness with which the works of Harvey, Jenner, Pasteur and Lister were accepted by the leaders of Medicine of their day, and in the hostility with which new ideas in the economic field have always been met by the followers of *laissez faire*. Original investigators who conquer the unknown generally receive their greatest recognition after they have passed on, but continue to receive it until the horizon becomes dimmed by time.

In this generation, progress has been made so rapidly in all fields of endeavor that even those who have added greatly to the sum total of our knowledge are apt to go unrecognized. We have many such who sit at the meetings of this Association. They walk among us so freely that we forget the contributions which they have made. We accept their gifts of knowledge with less ado than we accept gifts from friends; yet if a few score of these creative minds, with their contributions to science, were removed from the Medicine of the present generation, our profession would be comparatively barren of interest.

The members of the College have certain obligations to fulfill, not alone in Medicine but as leaders in this period of reconstruction which is upon us. A prime essential of leadership is an open mind, an ability to recognize the fact of an ever-changing present and envisage a future which will probably

be characterized by still greater change. One must be able to look forward for the solution to unsolved problems, not backward. The fundamentalist can not satisfy the inquiring mind of the present generation nor successfully solve the problems which confront it and future generations by looking back to the interpretation of moral and religious problems as given centuries ago.

TRENDS IN DEVELOPMENT OF PRESENT-DAY MEDICINE

The greatest advance which Medicine is making today is in the prevention of disease. The greatest advance in the domain of clinical practice is being brought about through a better understanding of its physiologic side. Until the immediate past, structural anatomy and structural pathology dominated the entire field. Symptoms which were unattended by recognized anatomical change were considered to be of no importance no matter how much they distressed the individual, and were ignored by able clinicians. Physicians regarded such symptoms with unconcern until sufferers began to seek aid from various irregular practitioners. This failure to grasp the importance of disturbed function is almost incomprehensible today, because the practice of Medicine is centered about a desire to understand the cause of symptoms, and to apply remedies which will relieve them.

Just when Medicine appeared to be definitely established on a structural basis, and organic lesions seemed to be secure in their occupancy of the entire stage of interest, a disturbing element entered in the form of new developments in the field of physiology. Advances in biophysics, biochemistry,

neural physiology and endocrinology came swiftly to the fore, and the importance of psychic reactions became appreciated as never before. We then learned that many of the symptoms which physicians are called upon to treat are changes in function without structural change in the organ showing the physiologic disturbance. We were then able to appreciate the ridiculousness of such statements as were current but a short time before to the effect that 90 per cent of the patients who visit doctors' offices have nothing the matter with them.

Physiologic studies emphasize the fact that the human organism is a united whole, in which the action of any one part may be influenced by every other part; and physiologic balance and imbalance now begin to assume great importance in the definition of conditions of health and disease. The cause, whether constitutional, environmental, structural, physiologic or psychologic, matters less than the fact that the patient is ill.

Approached from this angle, Medicine becomes a more rational study. It becomes both a physiologic and anatomic study. The fact that constitutional factors determine to a large degree the manner in which a given individual will react to environmental stimulus now becomes evident.

The nervous system, both somatic and vegetative components, each in its integrative action in its own separate field and in the interplay between skeletal and visceral structures now assumes an unexpected importance, not only because of its central reactivity to chemical and physical stimuli, but also because of its function in producing physiologic and pathologic reflexes.

Only by developing a more accurate knowledge of the vegetative nervous system can we understand the efficient correlating mechanism by means of which unity of action is brought about and maintained in distantly separated organs through centers in the brain and cord both during conditions of health and in states of disease.

Hormones, vitamins and salts, in normal proportions, as circulating regulators of cellular activity during health, and, in abnormal proportions, as disturbers of cellular activity during illness, become important determining factors in many aspects of physiologic and pathologic function. The electrical reactivity of cells seems to hold much in store for explaining body reactions, although as yet it is vague in the minds of most investigators. The pH of the tissues also bulks large in importance.

In physiologic Medicine, psychic reactions assume a prominence in the health of individuals which approaches in importance that of structural change, and which often proves to be of greater importance to their happiness. No matter what the disease, it has its psychic component which will either help or hinder recovery.

Physiologic Medicine is more difficult to comprehend and develop than anatomic Medicine, but medical science and practice can not be rounded out until this subject has been thoroughly investigated. It is more elusive and more erratic than anatomical studies. There are more variables in each problem. The field of study can not be embedded in a fixing solution and prepared for microscopic investigation. Physiologic reactions are subject to all changes which depend on inherited and acquired constitution, and on the adap-

tation of the living processes to environment in its broadest sense—both internal and external, both physical and psychical.

The rapid decrease in mortality in early life has permitted many with weak constitutions, who formerly would have succumbed to disease in infancy and childhood, to live and attain the age in which the human machine shows more plainly the effects of wear and tear, the age in which the degenerative diseases hold sway. This has forced Medicine to become increasingly interested in the patient as well as in the cause of the disease and the cellular changes produced by it.

Inherited qualities; physical and chemical constitution, as determined at birth and modified by environment; correlation and integration of activity through the hormones and nervous systems; and lastly the psychical structure of the patient now call for as full consideration as cellular pathology and the cause of infectious disease did but a short while ago. This shift adds a new, and in the minds of many men a greater, interest to Medicine.

Heredity, although its meaning was poorly defined, had been considered to play an important part in certain diseases prior to the time that their etiology was discovered; but, as specific causes, one by one, were discovered, heredity was forced for the time being to occupy an insecure position. With greater fundamental knowledge, however, we are learning that heredity plays some part in all diseases, and a very important one in many.

We assume that to attain old age one must be endowed with an anatomic and physiologic mechanism which adapts itself well to the work that it must do,

and meets the changing requirements of environment in a satisfactory manner; and further, that it does not become incapacitated by misuse, abuse or illness.

If the individual passes through early childhood, the chances are greatly in favor of his reaching adult life. Among those who attain adult life are many who are fit to live only because conditions have been made especially favorable for them. On the other hand, we must look upon the attainment of advanced age by most people as being due to a better, more virile stock. Captain MacMillan, the arctic explorer, once told the writer that the survivors of lost expeditions in the arctic were not saved by accident, as is commonly believed, but that their survival was evidence of a better heredity, a more rugged stock. He further said that nearly all such survivors, instead of having their bodies weakened by the exposures and hardships, endured them without apparent injury and lived to a "ripe old age".

SPECIALIZATION

One of the very interesting and important phases in present-day Medicine is the development of the specialist. While specialization is not new it has become a dominating characteristic of the Medicine of the last quarter of a century. It is the natural sequence of fruitful, systematic investigation.

With the rapid advance in knowledge at the turn of the century so many new facts were being brought forth that specialists became necessary in order properly to apply them to research and practice. When we behold the present highly specialized status of Medicine it is difficult to realize that

we are only one generation away from the general practitioner who applied, in treating the patient, all of the facts that were then known to all of the diseases that were recognized.

During the past quarter of a century keen observers have interested themselves in nearly every individual phase of Medicine; individual diseases, diseases of individual organs and systems, even symptoms caused by certain body reactions. They have set these subjects apart for special study, picking out the data which bear particularly upon the subject under investigation.

Individual men have chosen for special study those phases of Medicine which have appealed to them most, and so have added a sympathetic interest, which accounts for much of the rapid progress. Once started, the idea of specialization grew rapidly. It seemed impossible for single minds to comprehend and accurately weigh the new facts which were being added to the sum of medical knowledge and to apply them to medical subjects as a whole. Only through the study of limited fields was great success possible. By intensive specialization, in the short space of two or three decades, our knowledge of many subjects has been well systematized and our opinions and impressions have been replaced by facts.

We are today so accustomed to being directed and protected by the laws of public health, for example, that it seems as though this important phase of Medicine, calling as it does for highly trained specialists, must always have existed; yet the public health official had little scientific background and small reason for existence until the latter part of the nineteenth century,

when bacteriology developed and the theories that disease was due to supernatural powers and miasmas were displaced by actual proof of the cause of contagion.

Specialization during this developmental period threatened General Medicine with disaster. Its influence was largely disintegrative. It tore Medicine asunder, divided it up into many parts and attempted to create many separate entities. But strange to say this disintegration finally checked itself and resulted in a demand for a new assessment of values; for, as each specialty developed further it became more and more apparent that it was not a separate medical entity but only a part of Medicine as a whole, and a much more intimate part than some of the earlier specialists realized.

We now find that each specialty has resulted in enriching Medicine as a whole to the extent of its individual development; and Medicine, divided by the multitude of specialties during the period of their development, is now being reunited into a completed whole in which the internist is able to render a greater service than the specialist could give but a few years ago. That this process of unification and coördination is well under way is evidenced by the high character of service which is now being rendered by internists in fields which were limited to specialists but a short time ago.

Specialists will probably always be necessary, but their position will doubtless change. In the future the specialist, in the more restricted sense of the term, will probably assume the rôle of consultant in his particular line, and internists will specialize in those subjects which interest them predominant-

ly, but not to the exclusion of other phases of Medicine. In this way the narrowing tendency of specialization will be checked.

THE INTERRELATION BETWEEN MEDICINE AND GENERAL ECONOMICS

Much of the recent discussion of medical economics has not taken sufficiently into account the relationship of medical problems to the general economic condition.

The relationship which Medicine bears to the public was established before the birth of public health with its life-saving campaign and before the advances in science and technology were allowed to destroy the stability of industry. The logical solution of the problems of medical economics depends on the solution of the problems of general economics. If the state is to control industry, it will and probably should control Medicine. If, on the other hand, we are able to maintain the principle of individual effort in industry, it is but justice that the same principle should be applied to Medicine. Just at present, however, it appears as though Medicine were being forced to make an adjustment to an unadjusted and an admittedly unsatisfactory general economic system. If an open mind were ever needed in the solution of problems in Medicine, it is today.

The rapid development of modern Medicine has been made possible through advances in the cognate sciences. This in turn has called upon those desiring to practice Medicine or to engage in research to spend much time and money in preparation. It requires of the student who would fit

himself for the practice of Medicine an expenditure of from ten to fifteen thousand dollars, and the loss of earning power for the seven to ten years spent in study, a total of some \$15,000 to \$25,000.

While the cost of medical education has been increasing in recent years, changes have been going on within Medicine itself, as well as in our economic system, which tend greatly to alter the status of the profession; and, with present trends, to make its position in the body politic insecure. This situation is growing more and more serious, and must be carefully considered by present practitioners and prospective students.

Physicians are attempting to carry out principles of altruism, living ethical lives and following high traditions, in a competitive age which is characterized by uncontrolled ambition for profits. Laymen do not understand the motives which underlie the ethical acts of medical men. The aims and methods in Medicine are so foreign to those prevailing in business that it is impossible to furnish the laity with an intelligible explanation of our course of action. Were a business concern to foster methods which would limit its chances of economic success, the act would be looked upon as being not only foolish but one of insanity; were a business firm to refuse to take on a new purchaser because he was a regular customer of another firm, the act would be considered as contravening all business principles. On the other hand, were business concerns to adopt the altruistic spirit of physicians and take less profits, or no profits at all, from those who are unable to pay for their goods, it would soon change the

ruthless psychology which dominates modern economic life. Medical men do all of these things regularly as a part of their ethical standards.

Sentiment causes physicians to give their services to the sick poor without compensation. This they do gladly because they realize that they are not dealing with inanimate substances such as merchandise, but with human beings. Unfortunately, however, this very altruism exaggerates an already firmly established belief in the minds of laymen to the effect that medical service costs the doctor nothing, and that it is the province of Medicine to care for those for whom our present economic system fails to provide. Those ideas should be corrected, for they prevent the physician from being adequately compensated. Laymen should be made to appreciate that lengthened life, decreased morbidity and increased efficiency through relief from illness have a monetary value.

We shudder at the idea of State Medicine, yet under recent economic conditions during normal times the state furnishes medical care for a large percentage of the population, some justly, some unjustly, or at least questionably; as for example, veterans of the World War whose illness has no connection with service. Medical men vie with each other for positions on the staffs of charity hospitals where they give their services without remuneration. Many students of the subject put forth the argument that it is not fair that, of all services to the

poor, medical care alone should be furnished without cost. State Medicine, sick and accident insurance, unemployment insurance, old age pensions and group care are some of the many plans that have been suggested to insure adequate medical care to those who can not readily pay for it out of their earnings. Whether medical men are favorable to the idea or not, unless adequate changes are quickly made in general economics, some of these plans will be adopted. To the extent that they contravene the individual relationship between physician and patient they will be unsatisfactory; to the extent that they guarantee a better medical service to the people and give more adequate remuneration to the physician for services rendered they will be acceptable.

Perhaps there is no better way to obtain an idea of the problem of medical economics and no way better to judge the ability of people to pay for medical services than to study the incomes of groups of the population. Numerous surveys have been made, but I shall use the data obtained by the Commonwealth Club of San Francisco in 1931, and that acquired by the Committee on the Cost of Medical Care. Let me say, in passing, that conditions in San Francisco are much more favorable to the working classes than in many other cities of the country, for labor has had a large share in the government of this city.

The following is the grouping of incomes as brought out as a result of the San Francisco survey:

14 per cent of incomes were less than	\$1,000
30 per cent of incomes were from	\$1,000 to 1,500
35 per cent of incomes were from	1,500 to 2,000
14 per cent of incomes were from	2,000 to 3,000
5 per cent of incomes were from	3,000 to 5,000
2 per cent of incomes were over	5,000

If these statistics are analyzed from the standpoint of the population's ability to pay for medical care, it gives little comfort to physicians.

There is no fixed standard by which we may determine who can pay for medical services, and what the fee should be. It is supposed to be based upon the financial status of the patient, but this is determined not alone by the amount of a given income but by the demands made upon it. An unmarried individual without dependents naturally can pay a much larger fee than the head of a family with the same salary.

That portion of the population with dependents to care for, who receive salaries below \$1,500 a year, are not in a position to pay very much for medical care, for it is estimated that bare necessities cost about \$1,500 per year for a family of four persons in the larger coast cities. Unless more than one member of the family is working, those belonging to this group are forced to obtain most of their treatment in free clinics and public hospitals.

The 35 per cent of people with incomes from \$1,500 to \$2,000 with dependents to care for, should be able to finance ordinary illness requiring only a few visits of the physician, but long illness, or illness requiring the services of medical or surgical specialists, could not be financed except by markedly reducing the family's living standard.

Thus we have 79 per cent of the population of San Francisco, according to these statistics, who are unable when ill freely to consult physicians. This leaves 21 per cent of the people who might be considered as able to pay for medical care.

Now, turning to the findings of the

Committee on the Cost of Medical Care, we find that, based on a twelve months' survey made during 1928-1931, the combined earnings of the members of 50 per cent of the families in the United States amounted to less than \$2,000 a year, and of 40 per cent, amounted to from \$2,000 to \$5,000. Their report also shows that 80 per cent of individuals had incomes less than \$2,000; and 95 per cent, less than \$3,000. One fact which was brought out by the report is that 4 per cent of the families with incomes under \$1,200 per year, collectively, spent as much money for medical care as 80 per cent of the same families, collectively. This is discussed along with other findings and interpreted as showing that the uncertain cost of medical care and the inability of the people to meet such cost readily is deterring people with small incomes from freely consulting physicians. If medical care is a necessity, however, as we certainly believe it to be, this should be interpreted as showing that people do not have sufficient income to pay for the necessities of life, and should call for adjustments in general economics rather than sacrifice on the part of physicians, for the same people are unable to supply themselves adequately with other necessities such as food, clothing and shelter.

Public health and sanitary science, by creating a better environment to live in, have protected and strengthened the race, lowered the incidence of disease, and markedly reduced mortality. Based on these facts optimists have dared to express the hope that infectious disease may be eliminated from the face of the earth. Whether such a desideratum may or may not be accomplished, at least every increase in bac-

terologic and epidemiologic knowledge, and every advance in sanitary practice brings such an accomplishment nearer of attainment; and, simultaneously, restricts further the field of medical practice.

General mortality has been reduced 50 per cent during the past 50 years. infant mortality 60 per cent in 20 years, and life expectancy has been increased from 40 to nearly 58 years in the past 40 years. Where only one-half of the population could expect to survive the eighteenth year one hundred years ago, one-half of those born today may expect to live to be 66 years of age; and one-fourth, 76.

While the population, as a whole, has greatly profited by these accomplishments, medical practice and economics have undergone changes which demand readjustment. Physicians have been deprived of a large source of practice among children whose medical care is paid for by parents during the most prosperous period of their lives. They find themselves instead treating an ever-increasing number of older people during the period of declining efficiency, when their earning power is decreasing and when, too often, they have already reached a state of dependency. Also they find themselves treating an increasing number of people with small incomes and an increasing number of the unemployed.

The reduction in illness and mortality in early years, and the rapid increase in life expectancy, have not only brought about important changes in the trends of study, practice and economics of Medicine, but at the same time have exerted a definitely disquieting influence upon the general economic

condition of the country. These influences are so subtle that they have scarcely been appreciated, and therefore have not received the attention which their importance demands.

At first glance it would seem that the effect of an increasing number of people reaching adult life should be favorable to medical practice, and this would be the case if continuous employment at adequate wages were obtainable for all, so that physicians might be freely consulted when sickness arises; but, unfortunately, the number of people who are competing for employment is increasing at a time when, on account of the changes in our industrial system, fewer workers are required. Chase says that every census for an hundred years showed an increased number of men in the factories until the late war, after which production has gone steadily up, increasing 70 per cent between 1914 and 1927 with the number of employees as steadily decreasing. While 1929 was the peak year of production in industry in the United States for all time, yet there were one million and a quarter more workers idle than in 1923. We are saving lives and enabling men to live to old age, but are not making provision for them in our economic system. Therefore, increased longevity may prove to be a curse to those who attain old age, and it may throw an added burden on the physician in the way of more illness to care for without increase of his compensation.

As has been seen, workers who receive \$1,500 and less per year represent a very large proportion of our population. As an example we cite the shoe industry, which in 1925 paid an

average annual wage of \$1.090 per worker. Workers reach their highest earning capacity at the age period of 43 to 55, after which their earnings decrease; and since the earnings for most of this class have been barely sufficient for necessities during their most productive period, savings for sickness and old age have been scant or have amounted to nothing at all.

We may appreciate the effect which a shift of a large portion of the population to the higher age periods may have upon the medical profession, and also on the general economic condition of the country by determining the proportionate changes which the percentage of the people in the various age brackets has undergone in recent years. Fortunately we have for comparison the statistics of 1870 and 1920.

In 1870, when mortality in childhood and adolescence was high, the death rate was so great that 49.5 per cent of the population was in the age period from birth to 19 years. By 1920, largely through the application of preventive health measures, so many more people had already lived through childhood and adolescence and passed on to adult life that only 40.3 per cent of the total population were found between the ages of birth and 19 years. In the same 50 years the percentage of those between 20 and 44 years had increased from 12.6 to 16.9 per cent, and those above 65 from 2.9 to 4.5 per cent of the population.

The significance of this shift may be clearly seen by reducing the changes to percentages of the 1870 population.

During the 50 year term, the percentage of the total population included in the age-group from birth to 19

years decreased 19 per cent. The percentage of the population from 20 to 44 years, during these same 50 years, increased 9.4 per cent; giving 9.4 per cent more workers for whom employment must be provided during this most productive period of life. Those from 45 to 64 years increased 34 per cent, furnishing another very large group for whom work must be found; and those above 65 years increased 55 per cent, more than doubling the number of people in this period in which dependency and illness are most frequent. During this same period immigration also brought many workers into the country to compete for employment.

The shifting in age groups will become still more serious when, as we are told by statisticians, in a few more years our population becomes stationary and the younger group will constitute only about 30 per cent of the population, while 10.7 per cent, an increase of 138 per cent over the figures for 1929, will be over 65. The stationary period in the growth of our population will be hastened by the stop which has recently been put to immigration. Industry must take this reduction in purchasing power of future domestic consumers into consideration.

In order more fully to appreciate the interrelation between medical and general economics, we must examine the changes which have been wrought in our general economic system and the factors which have been responsible for them.

For four thousand years prior to the discovery of steam power there had been practically no change in man's productivity. Handicraft ruled the

world. There was no machine problem. There were no labor crises. There was no game of industrial warfare.

Steam ushered in a new era, and caused machines driven by the new power to compete with handicraft. In these early years the machines were thought to be inventions of the devil and were feared by the workers; but none realized the extent of the economic changes which were to be brought about by them in a fully mechanized age.

In the middle of the nineteenth century the effect of steam on industry was well established. At first machines were confined to a few industries and to industrial centers, and invention was directed toward increasing the production of those things which were necessary for man's welfare. The result was a ready consumption at home and available markets nearby for the surplus. This was the dawning of a new era in which human comforts were increased, and a new plane of living was ushered in.

Modern science, however, has made invention a plaything, and the world the market for its produce. Machine after machine has been invented, the sole aim of which has been to make more goods, not necessarily because they were needed, but because they offered profit to the inventor and those who were associated with him in their manufacture. Production is no longer wholly directed toward supplying man's needs, but toward supplying luxuries and satisfying man's whims. With special high-pressure salesmanship adapted to each article, accompanied by installment buying, almost anything has become salable, and people of mod-

est incomes have enjoyed comforts and luxuries as well as necessities.

Man power up to the time of the introduction of steam was considered to be equal to one-tenth horse power. On that basis the energy value of the adult male population of the United States today would be 3,600,000 horse power, but it actually is 1,000,000,000 horse power.

Many statistics of machine efficiency have been cited in current literature to show the extreme to which man power displacement has gone. These are passed over as fantastic by the more conservative; they are accepted at face value by the radicals; and are being considered as worthy of impartial investigation by a large mass of our people. While these statistics have been criticized by some investigators as being incorrect in certain details, that they are correct in principle is not questioned, and that our social and economic systems have not taken sufficiently into account the unemployment caused by the machine, nor made adequate adjustment to the various changes which the revolution in industry has brought about, is also unchallenged.

The following examples will illustrate the point:

For centuries one man could make about 450 bricks in a day; today a modern brick plant will make 400,000 bricks per man per day. For centuries a man could make one and a half barrels of flour per day; a modern flour mill will make 30,000 barrels of flour per man per day. The flour industry in 1899 was represented by 9,000 plants, employing 32,000 workers and utilizing 471,000,000 bushels of wheat. The number of plants increased to

11,700 in 1909; but in 1929, the number had been reduced to 2,900, employing only 26,400 men but utilizing 546,000,000 bushels of wheat. In 1900 the steel industry in the United States produced 11,000,000 metric tons of steel, requiring an energy of 600,000,000 man hours, which was equal to 70 man hours per ton, in 1929 the industry produced 58,000,000 tons, using 770,000,000 man hours, or at the rate of 13 man hours per ton.

So it goes on down through the whole field of industry; one man and a machine doing the work of many, and casting off those who are displaced to find new jobs or to join the unemployed. Each advance in science, and each new invention, makes adjustment in the established order necessary and opens up new possibilities for further scientific advance and invention. This calls not only for readjustment in industry, but in the social and economic spheres as well. It is not rational that science and invention should work harm to civilization, but by the failure to make proper adjustments the very foundations of our social and economic systems are being threatened. Did the late President Roosevelt have an inkling of what was going on when in 1918, to the query as to how long the present government of the United States would last, he replied: "Not to exceed fifty years".

The above striking illustrations of modern mechanization by no means reveal the end of technical possibilities. They show the inevitable trend of invention and mass production toward the displacement of men, but so long as existent industries, or industries newly established, were able to absorb

the displaced workers readjustments were effected. During the past decade, however, regardless of the establishment of new industries, unemployment has increased. Unfortunately, invention is displacing the skilled artisans and putting industry in the hands of machines and unskilled workers. While the products may be better, the machine has become the producer and the skilled worker has been degraded.

The present-day program of industry aiming at mass production also calls for large combinations of capital to insure distribution. It drives owners of smaller, independent businesses to the wall because of their inability to compete with larger companies, a policy which is rapidly eliminating the great middle class, the class which has shown the greatest appreciation of medical service and has given physicians their surest and most satisfactory return, the class which has always been recognized as the backbone of democratic nations. The independent merchant, the small manufacturer, and the farmer who owns his farm are being displaced one by one, for they have no place in the new order. They have been ruthlessly crowded out of the picture with nothing to compensate them or the nation for their loss. If the middle class is to have no place in a thoroughly mechanized society, then something must be devised to take its place. No people can be happy, nor can a nation long endure, if only a small percentage of the population who control industry are independent, while the rest are dependent upon them.

The rapidity with which production is shifting to large corporations is amazing. The small unincorporated

manufacturer does only 5 per cent of the manufacturing of the country today. In Illinois, in 1909, the individual owner employed 10 per cent of wage workers; and in 1919, 5.5 per cent, a decrease of nearly 50 per cent in 10 years. In the same state, in 1928, the net profits of all incorporated manufacturers was \$5,280,000,000; that of individual manufacturers was \$210,567,000, only 4 per cent of the total. This tells the story of the small independent manufacturer. Add to this the story of the independent farmer. We have boasted that American farmers alone in all the world have never been of the peasant class; but during the twenties, when all industries exclusive of agriculture were having the most prosperous years ever known, the farmers were in dire distress, were rapidly losing their farms and independence, and were sinking into a state of despair. The average net income of the 6,668,681 farms in 1929, for use in meeting the expenses of "capital, management and family living," was only \$847 per farm; and this had dwindled to \$342 per farm in 1931, and was probably about 25 per cent less in 1932.

Mass production, governed by competitive regulation, affects the employer as well as the worker, the difference being one of degree. It forces costly changes in productive plants, that each may be kept at the highest production efficiency, and is responsible for recurrent periods of saturated markets followed by inevitable unemployment, and shrinking in capital values. In 1929 there were 2,250,000 workers idle and 513 persons with incomes of over \$1,000,000 reported in the United

States; in 1931 there were 11,000,000 workers idle and 75 persons with incomes over \$1,000,000; while at the present time it is estimated that there are 14,000,000 workers idle and an equal number working only one-half time, with only a few individuals having incomes of \$1,000,000 a year.

Inventive genius and the genius to establish large combinations of capital in production and distribution, if uncontrolled, can produce only industrial instability and social unrest; if properly guided, on the other hand, they could be made into forces for a greater civilization.

The fact that the number of people above 65 years of age has increased so markedly in recent years requires that our economic system make adequate provision for workers both during their productive period and in their declining years; otherwise, public health measures become a mockery, and work an injury rather than a blessing.

The following statistics show with what rapidity unemployment is increasing in workers beyond 65 years of age. In 1890, 26.2 per cent of the male population over 65 years of age was idle; in 1920 the percentage was 39.9 per cent, an increase of 52.23 per cent in 30 years. We have no statistics at hand which give the amount of forced unemployment among the older workers which took place preceding 1929. We do know, however, that in 1929 there were 2,250,000 wage earners idle in the United States, an increase of more than 1,000,000 over the number idle in 1919; and we further know that the age group above 40 contributed more than its natural proportion to this

number, and that the proportion of those above 65 was likewise very exaggerated.

The increased amount of illness which affects those of the higher age groups makes it much more difficult for them, when once they lose their positions, to secure employment again. For those beyond 65 it becomes almost impossible. Even the insurance against illness which is supposed to work in favor of the employee works against the older man, for he is too apt to become a beneficiary to make him profitable to the employer, or to the insurance company.

Businesses of all kinds recognize that young, alert workers are able to accomplish more than those in declining years. While age may bring with it an improved judgment, modern technology leaves little place for judgment on the part of the worker. In vast commercial combinations judgment is furnished by overseers with exceptional technical training; very often by men who have no interest in the organization for which they work, except that of salary. The particular ability which calls for special monetary reward in the present economic system is that of supplying capital, organizing the business and choosing trained experts to do the technical work.

Since the economic prosperity of the nation depends upon maintaining the proper balance between production and consumption, we can turn back and hear the death knell of prosperity sounding a decade before the crash of 1929 came; but it fell on deaf ears. Productivity was fast outstripping wages. It had increased 54 per cent but wages only 30 per cent between

1900 and 1925, and by 1929 productivity in manufacturing had increased 90 per cent and wages only 40 per cent. Even with this enormous productivity manufacturing plants were running at only 60 per cent of their capacity. Such a divergence between productivity and wages caused a corresponding lag in consumption of goods which could only be remedied if those who received the difference in remuneration should consume the excess in goods, or failing this, if the commodities should be absorbed in foreign markets; neither of which was possible.

Since mass production calls for mass consumption, every idle man causes the loss of the consuming power of himself and those dependent upon him. If the 40,000,000 or more idle men in Europe and America, of whom at least 14,000,000 are in the United States, could be put to work at reasonable wages today, their consuming power would start all essential industries going. Indeed, what can start industry going other than an increased demand for goods? A prominent industrialist, keenly interested in the unemployment situation, recently stated that on account of the increased productivity which has been brought on by our modern industrial methods, we shall not have full time employment for our 48,000,000 workers in the United States for some years to come, probably never. Such a statement, if true, calls for complete industrial readjustment.

A machine driven by one man may do the work of ten or twenty men, and many will do that of a hundred; yet even so, there may be an enormous loss to the employer as well as to the workers who are thrown into the un-

employed ranks, unless, at the same time, provision is made for the consumption of the goods which the displaced 9, 19, or 99 men, with their families, would have consumed.

The most dependable market is made by employed workmen. They are far more important as consumers than the 2,000 directors of the 200 corporations in the United States which are said to control from 35 to 45 per cent of the business wealth, for the latter can not consume from 35 to 45 per cent of the goods produced.

Crises have recurred periodically since machine power became prominent in industry, but have become more frequent and more severe as efficiency in production has increased, and as world problems have become more complex. The aftermath of the World War has been partially responsible for the severity of our present economic crisis, but not the cause of it. Nevertheless international adjustments would greatly facilitate economic recovery. Many believe, with Lloyd George, that the present is not just one more recurrent depression but an indication of the total breakdown of our social and economic systems.

The United States has about 6.2 per cent of the population of the world, but it has 50 per cent of the world's energy. It has been calling upon its natural resources; its forests, coal, oil, natural gas and iron with unpardonable prodigality. It has ignored its agricultural class until it has driven the farmers to ruin. It has been the most active nation in applying science and invention to industry, hence has shifted the major portion of its population from the country to the city. It has

equipped its manufacturing industries so as to be able to produce enough goods for a great proportion of the world's population. In its mad onward rush it has neglected to make necessary adjustments in the social and economic life at home, and has also failed to take sufficiently into account the fact that other nations were also taking advantage of science and invention and equipping their industries for satisfying most of their own wants, and were also bidding more and more for foreign markets. So, just when equipped for an unwarranted production of goods, markets were found wanting, and industrial stagnation supervened.

During crises workers suffer a reduction in wages and lose their positions, capital becomes unremunerative, industrial plants remain idle and deteriorate, and distributing systems cease to function. Depressions are spoken of as inevitable. They are no more inevitable than the plagues of old. They call for scientific investigation and purposeful action; not mute acquiescence. They may be prevented if an altruism which recognizes human rights as being supreme, and the opportunity to supply the necessities of life by work as being an inalienable God-given right is made to pervade the industrial and economic world. Every man who wants to work should have employment. We must get away from the idea that every man in industry who can not do the maximum amount of work is waste. Every man is a potential consumer of goods, and all else being equal the larger the salary of the working man, and the more workers employed, the greater the consumption of goods, for their weekly incomes

represent their weekly expenditures. Every idle man, on the other hand, is a burden on some one, either temporarily or permanently.

The requirements of greater combinations of capital which characterize the "machine age" have put into the hands of the bolder and keener business men an undreamed of opportunity for the accumulation of profits and hoarding of wealth. These men by nature are neither worse nor better than the small manufacturers, merchants, and workers whom they have displaced. It is not against men that remedial measures are to be directed, but against the system which fails to recognize the rights of all men. Stripped of its glamour, the accumulation of great wealth is neither necessary nor desirable. It gives an unnecessary advantage to its possessor which few, if any, are able to use wisely, and worst of all creates an aristocracy based on power to command rather than on ability to do.

Many remedies for our present economic maladjustment have been proposed, each attempting to satisfy certain principles held most important by the one who makes the suggestion. Is it to a new order that we must look, such as socialism, communism, or fascism; or may a satisfactory solution be brought about, as many of us hope, through a modification of our present capitalistic system which will make it meet the requirements of the population as a whole, giving collective protection while preserving individual effort?

It is evidently impossible to make the same economic ideas that we held a century ago fit into the new order which has been ushered in by modern

science and invention. We must not try to cure a body politic suffering from systemic infection by directing our attention to a single organ. We must have the body economic examined by the most competent specialists to be found, and when they have catalogued and analyzed the symptoms and arrived at a comprehensive diagnosis, have our statesmen devise effective remedies, which will permit each social and economic group to develop to a maximum degree and render the best possible service to the people. It is useless for Medicine or any other single group to attempt to adjust its affairs to the present unsatisfactory general economic state; on the other hand, it is the duty of Medicine to join with other social and economic groups in bringing about a complete reappraisal of our entire social and economic system.

The experience of Medicine by which it was removed from the chaos caused by belief in spontaneous generation and miasmas, and in a brief space of time put upon a scientific basis by a few great leaders, such as Virchow, Villeman, Pasteur, and Koch, should suggest the way out of our economic distress. Leaders alone, however, can not produce the results. It requires followers possessed of open minds in whom the spirit of progress is held in greater esteem than are established opinions. General economics is still in the age of plagues and miasmas. It is waiting for a scientific awakening. It is calling for statesmen with the same originality as that shown by our great leaders in Medicine. Such leaders must be imbued with the same belief in human rights which has actuated those who

have met other great crises in history. The rights of all people must be paramount, and more "golden rule" and less "gold rule" must enter into the solution.

The scientific methods which have been applied to modern industry should guarantee to all of the people of the world a greater degree of economic security and the continuous enjoyment of a better health, a greater happiness, and a higher type of physical and cultural attainment than has ever before been possible. Unfortunately, however, we have been rushed from one

achievement to another with such precipitous haste that we have failed to adjust our progress to man's requirements. We are idle in the midst of the greatest producing devices in the history of the world; we are hungry and cold in the midst of abundance of food and clothing; and the wheels of industry are blocked although backed by the greatest concentration of wealth known to man. How to harness science for the good of mankind and not allow it to run on to his debasement and destruction is the burning question which this generation must settle.

Observations on Addisin in Diseases of the Blood*†

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IT has been demonstrated^{1,2} that the normal stomach in man, swine, dogs and cattle secretes an hemopoietic substance which, when properly concentrated and purified, may be injected intramuscularly into man. This substance is thermolabile, dialyzable through celloidion, and exhaustible, and may be converted to an ethyl ester and extracted with non-aqueous solvents (ether, acetone, chloroform) without impairing its hemopoietic activity. These properties, which characterize both the material obtained from human gastric juice and that from the gastric contents of swine, practically exclude the possibility of its being an enzyme. It is probable that it is a physiological hemopoietic hormone, for which we have proposed the name *addisin*. Without sufficient evidence to enable one to arrive at definite conclusions, it seems likely that *addisin* is identical with the "intrinsic factor" of Castle³ and with "hemopoietin" of Wilkinson,⁴ a substance expressed under high pressure from the stomachs of swine.

Practically pure gastric juice has

been obtained from man through a stomach tube and from dogs through a gastric fistula. Such gastric juice, without an "extrinsic factor" such as beef or vitamin B₁₂, when properly concentrated, gives a prompt hemopoietic response following intramuscular injection in a patient with pernicious anemia. There is no noteworthy histologic change at the site of injection in man and in rabbits (figure 1 (B)), and we believe, therefore, that an "extrinsic factor" is not essential in parenteral administration.

METHODS OF PREPARATION

Various methods of preparing gastric juice and gastric contents for intramuscular injection have been tried. Concentration by evaporation is unsatisfactory, but (a) concentration *in vacuo* yields an active product. *Addisin* in active form has also been obtained (b) by preliminary concentration *in vacuo*, dialysis, and further concentration *in vacuo* of the dialysate; and (c) by esterification of the concentrate obtained in either of the two preceding methods. A paper giving the details of these procedures is in preparation.⁵ As yet, we do not know which method yields the most active product. In each of the methods hy-

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drochloric acid has been neutralized *after* concentration. Sodium hydroxide, sodium bicarbonate or a saturated solution of disodium hydrogen phosphate has been used for neutralization of the acid. Enough is added to render the mixture faintly alkaline to litmus. With

temperature of the gastric contents be kept below 37°C. in any of the procedures mentioned above.

DOSAGE

To establish a rough measure of dosage, we have designated as *one unit*

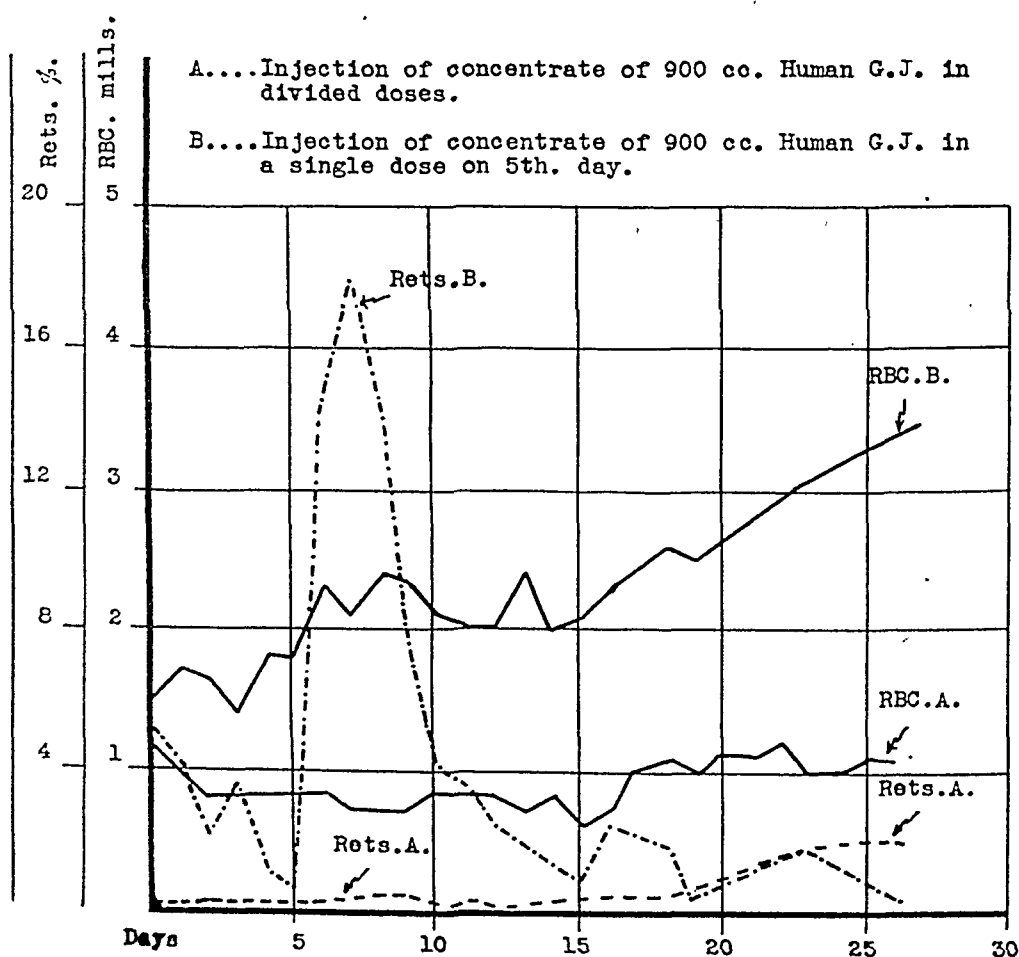


FIG. 1. A. Percentage of reticulocytes and red cell count following 9 units of human gastric juice in *divided* doses. B. The same following 9 units in a *single* dose.

aseptic precautions, the final product is usually sterile. When contaminated, however, the neutralized concentrate is diluted with four volumes of ethyl alcohol. The mixture is then passed through a Berkefeld filter, and the filtrate is collected in a sterile flask. The alcohol is readily removed by distillation *in vacuo*. It is important that the

of addisin the material recovered from 100 c.c. of original gastric juice or gastric contents. It has been found that repeated small injections are less effective than a single large dose (figure 1). Thus, the administration in divided doses of 9 units of addisin (human) has failed to produce the hematologic response in pernicious

anemia which later followed a single injection of 9 units in the same patient. Analogous results have been obtained with addisin from swine.

The hematologic response to addisin prepared by each of the three methods

shown definite evidence of hemopoietic activity.

Large quantities of gastric contents may be secured at slaughter houses from swine and cattle. Unlike the pure gastric juice obtainable from man or

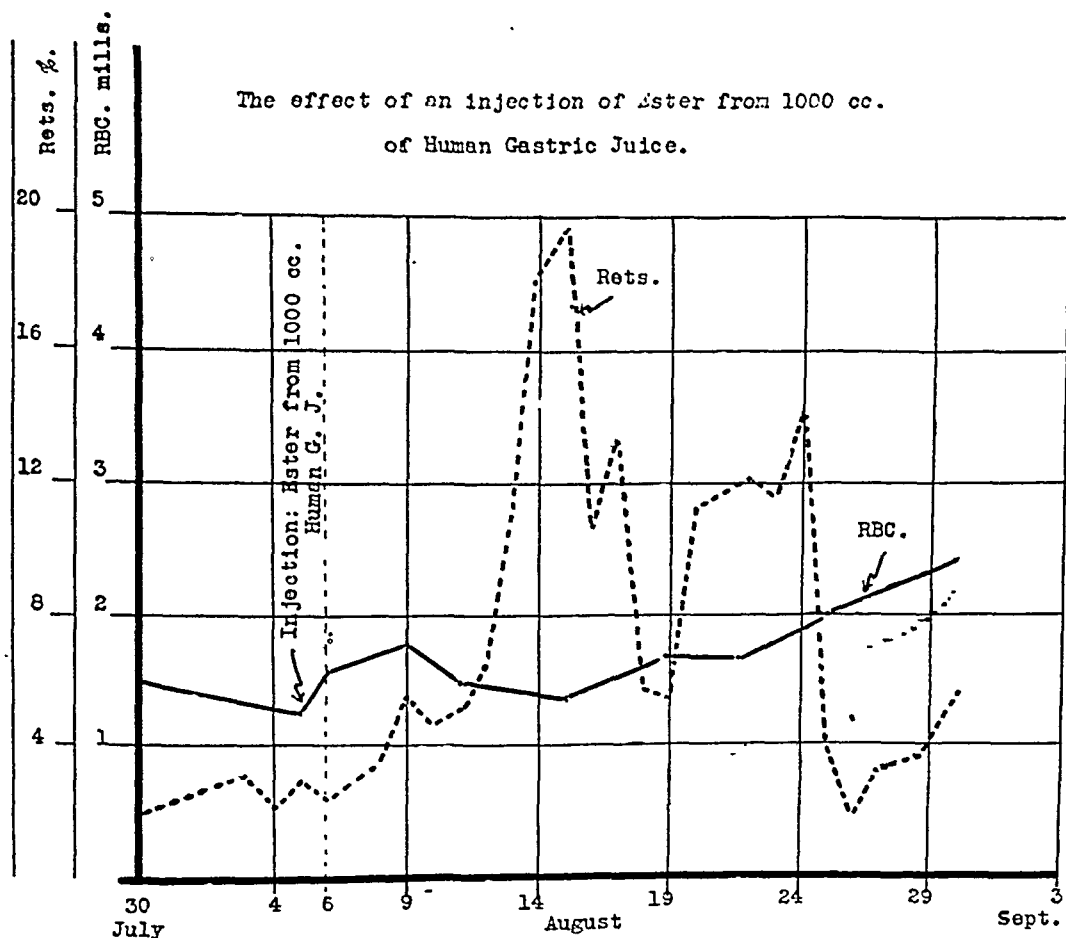


FIG. 2. Percentage of reticulocytes and red cell count following the injection of 10 units of ethyl ester of human gastric juice.

referred to previously is prompt in pernicious anemia. The product obtained by concentration *in vacuo* of human gastric juice and its ethyl ester each cause reticulocytosis and maturation of the red cells (figures 1 (B) and 2). Studies with the dialysate of concentrated human gastric juice have also

from dogs with a gastric fistula, the gastric contents of swine and cattle contain food in various stages of digestion. This material is analogous to the gastric juice plus beef or vitamin B₂, as employed in Castle's experiments, but the material obtained from its concentration gives a response in

every way similar to that obtained from concentrated human gastric juice without an extrinsic factor.

PERNICIOUS ANEMIA

Remarkable hemopoietic responses in pernicious anemia have followed the

globin from 47 per cent to 93 per cent (figure 3). A second patient with pernicious anemia received 57 units of concentrated swine gastric contents. The immediate effect was a blood crisis lasting 24 days and a reticulocytosis of 44 days' duration. Without other

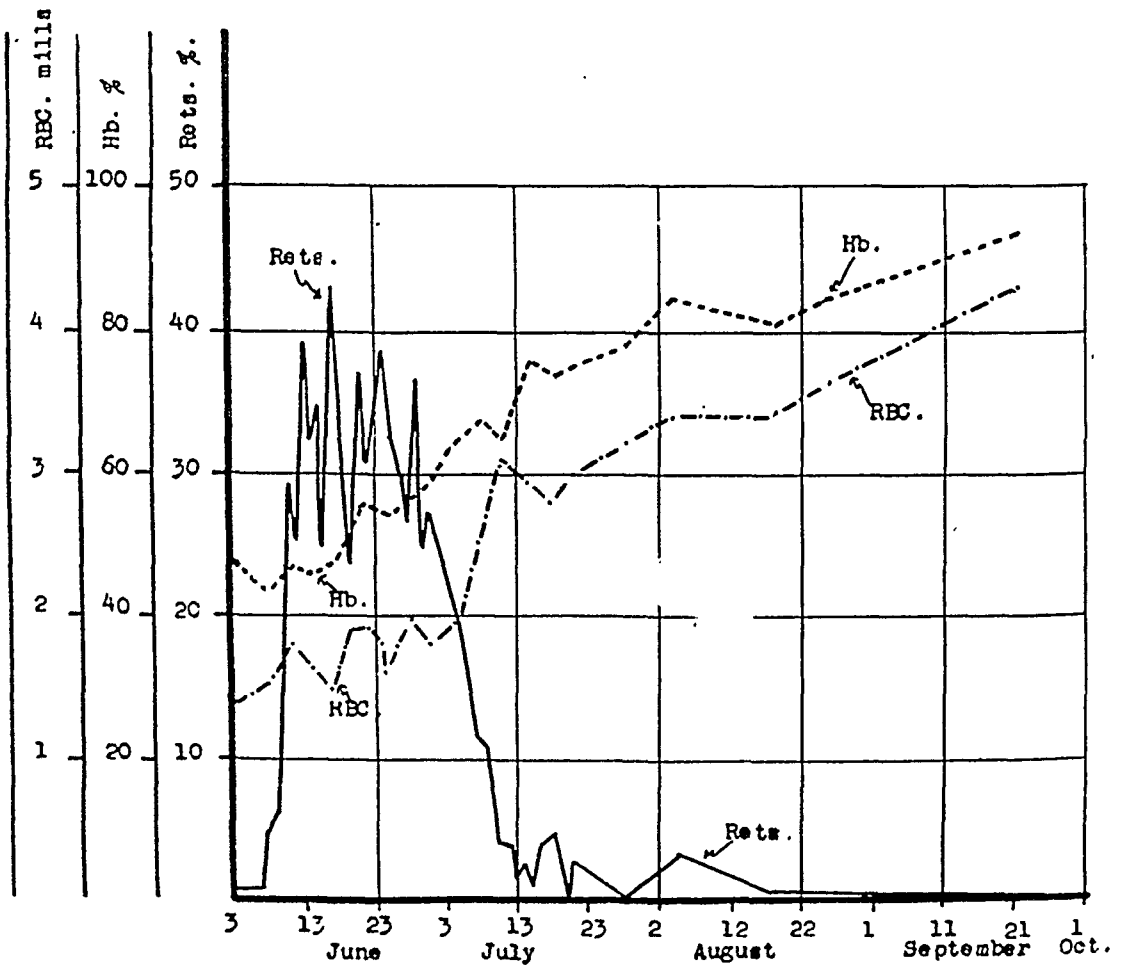


FIG. 3. The hematologic response following a single dose of 30 units of the ethyl ester of swine gastric contents.

use of single large doses of addisin obtained from swine. The injection of 30 units of esterified concentrate resulted in a prompt reticulocytosis of 24 days' duration, accompanied by a blood crisis during the first 12 days. In the course of 115 days, without further treatment, the red count rose from 1.4 million to 4.5 million and the hemo-

treatment, there was a rise in the red count from 1.5 million to 4.2 million and in hemoglobin from 44 per cent to 80 per cent in the course of 64 days (figure 4). From patients now under observation, it is probable that similar results may be expected with addisin obtained by dialysis and also from the esterified dialysate. Following intra-

muscular injection of a large dose, the greater part of the addisin may be transported to the liver for storage, though proof of this is lacking.

Studies on addisin in the gastric contents of cattle are not advanced to

the filtered gastric contents of cattle ten minutes after slaughtering. Their results are analogous to those reported by Castle³ and his co-workers with oral administration of human gastric juice incubated with beef or with vitamin

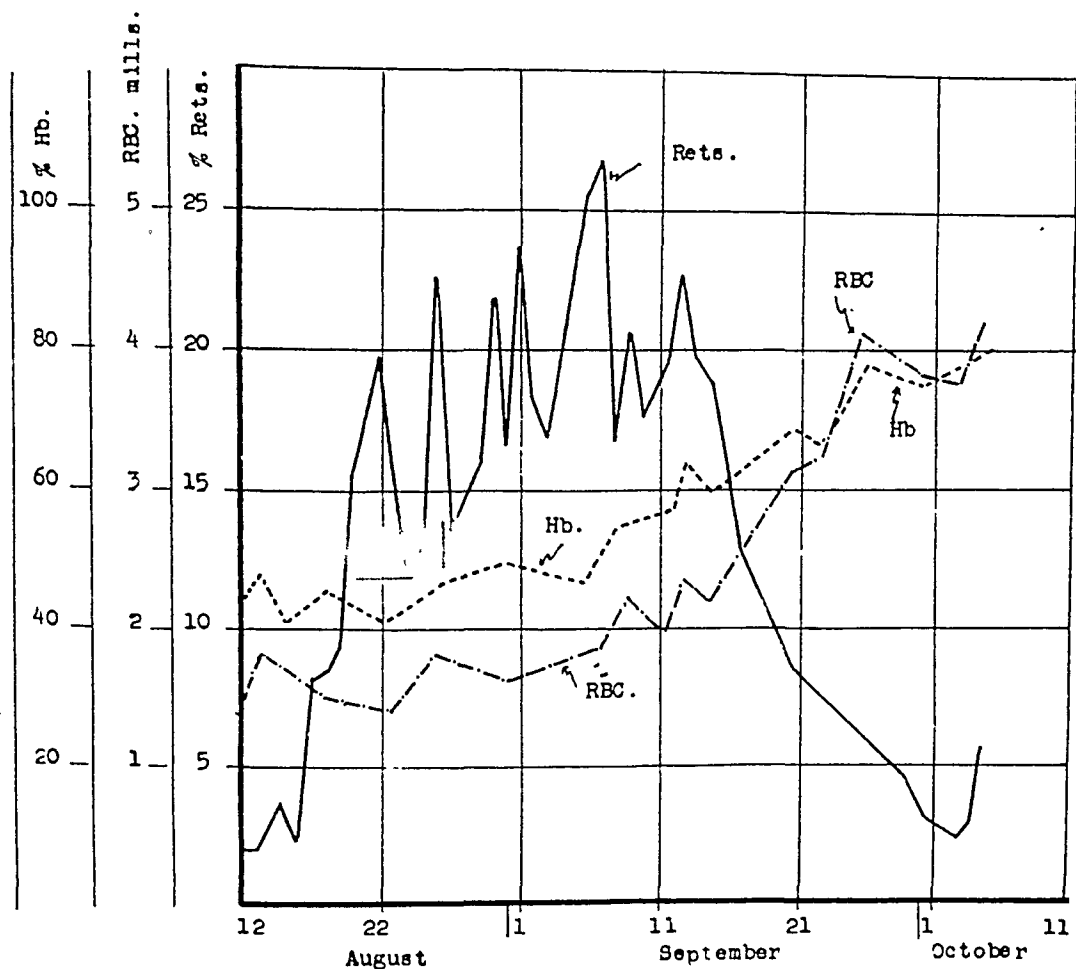


FIG. 4. The hematologic response following a single dose of 57 units of concentrated swine gastric contents.

the point we have reached with material from man and swine. There is, however, definite evidence of hemopoietic activity following intramuscular injection of the concentrate of the gastric contents of cattle. Williams and Vander Veer⁵ have obtained a remission in pernicious anemia in four patients by the oral administration of

B₁₂. In the light of these positive findings, it is surprising that Wilkinson⁶ was able to obtain no response from administering preparations of the stomach tissue of cattle.

To date, five patients with pernicious anemia in relapse have received injections of concentrated human gastric juice and eleven have been given con-

centrated swine gastric contents. In each, a reticulocytosis was produced. The earliest response was within 10 hours, the latest within 5 days. In Conner's⁷ patient, treated with human gastric juice, the reticulocytosis appeared on the tenth day. The best results, as judged by height and duration of reticulocytosis and blood crisis and by maturation of the erythrocytes, have followed the single injection of 30 to 60 units of potent material obtained by concentration *in vacuo* of swine gastric contents and by the esterified concentrate. An inadequate supply of material secured by dialysis has thus far prevented a comparison of potency with the other preparations.

Symptoms of shock, possibly due to histamine, have developed promptly on attempts to administer, intravenously, concentrated gastric contents (both from man and from swine). With our present preparations, intravenous use is dangerous and is not employed. With most of the preparations we have used, intramuscular injection has caused only a minor local reaction and little or no general reaction. Before injecting, it is important to be sure that the needle has not entered a vein. No anaphylactic phenomena have occurred.

ERYTHREMIA

Erythremia (polycythemia vera) is in many respects the antithesis of pernicious anemia. The etiology is unknown. In this disease there is a normoblastic marrow in contrast to the megaloblastic marrow of pernicious anemia. Theoretically, most of the changes observed in this disease might result from a hypersecretion of addi-

sin or from a hypersusceptibility of the bone marrow to stimulation.⁸ A patient* with 8.9 million erythrocytes was given 12.5 units of addisin (swine). The immediate response was a reticulocytosis of 2.5 per cent and 14,700 red cells per cu. mm. containing minute nuclear particles. The latter is a reaction to addisin which we have observed repeatedly in pernicious anemia at the onset of the reticulocytosis or just preceding it. In the patient's blood, none of these cells was found prior to the injection of addisin. A week later they had disappeared. A patient with pernicious anemia, refractory to liver extract intramuscularly, whose red count was 4.1 million, received 3 units of addisin (human). A reticulocytosis of 2.7 per cent and increase in red cells containing nuclear particles to 6,500 per cu. mm. appeared promptly, followed by a rise of the red count and hemoglobin to normal. The numerical response of reticulocytes of the patient with erythremia was twice that of the patient with pernicious anemia (table 1). However, differences in dosage and in preparations may account for this. The bone marrow of a second patient with erythremia showed a similar response to addisin.

It is a matter of interest that the first patient with erythremia has also had a duodenal ulcer. He has kept careful records of his blood counts over a period of years. In June 1930, when the red count was 10.0 million, he began gastric aspiration at 9:30 p. m. and lavage three to four times

*We are indebted to Dr. D. P. Abbott of Chicago for the opportunity to study this patient.

each week and continued this until the following December. Without other treatment, there was a steady decrease in the red count to 5.3 million. The lavage was discontinued in December, and in the course of the next few months the count rose again to 10.2 million. The lavage three to four times weekly for a period

cytosis, which is permanent in acholuric jaundice, is seen temporarily in pernicious anemia in response to liver and its derivatives, to ventriculin and to addisin, and in spontaneous remissions. In pernicious anemia, the low red count is due chiefly to failure of both production and maturation of the erythrocytes. In acholuric jaundice, on

TABLE I
MAXIMAL RETICULOCYTE RESPONSE TO ADDISIN IN REMISSION
OF PERNICIOUS ANEMIA AND IN ERYTHREMIA

Disease	No. of red blood cells	Percentage of reticulocytes	No. of reticulocytes
Pernicious anemia	4.1 million	2.7	110,700
Erythremia	8.9 million	2.5	212,500

of six months must have removed an appreciable quantity of addisin from the stomach, a fact which we believe supports our theory and may explain the return of the blood count to a normal level. Through the action of drugs and roentgen-ray exposures over the stomach, as well as by repeated injections of histamine, we have attempted to lessen the secretion of addisin and so to improve the condition of the blood. As yet, we have not met with success.

ACHOLURIC JAUNDICE

Acholuric jaundice is a disease with characteristic hematologic findings. In certain respects, the qualitative blood changes are similar to those seen in pernicious anemia. The increase in the bilirubin of the serum and of urobilin in the urine in each of these diseases is generally attributed to increased destruction of the red cells. The reticulo-

the other hand, lack of normal maturation of the red cells may be an important factor in causing the anemia. Theoretically, it would seem possible that addisin might promote maturation in this disease. If so, one would expect a *decrease* in reticulocytes following its administration in acholuric jaundice, — a reaction the reverse of that seen in pernicious anemia.

There has been opportunity to study the effect of addisin in only one patient with acholuric jaundice. Daily reticulocyte counts for a period of two months showed a variation between 11.6 per cent and 23.1 per cent. The mean percentage for this period was 15.8. On December 19th, 30 units of addisin were given. Three days later the reticulocytes had decreased to 8.9 per cent and at the end of five days the minimum of 6.7 per cent was reached. The percentage was relatively low for the next six days (figure

5) and then rose. This lot of addisin, when given to a patient with pernicious anemia, was found to be of low potency. It caused a reticulocytosis which was maximal on the fifth day. In the patient with acholuric jaundice it may be significant that the *minimal* percentage of reticulocytes occurred also on the fifth day after the injection.

A second intragluteal injection of 55 units of this lot of addisin was given on January 20th, when the reticulocyte percentage was 11.5. On January 23rd, the percentage had decreased to 5.8 and on January 25th it was 6.6 per cent.

The decrease in reticulocytes soon after each of two doses of addisin is significant of an effect on the bone marrow and indicates the possibility of establishing better, perhaps normal, maturation in acholuric jaundice through the use of more potent preparations. Studies on the fragility of the erythrocytes and bilirubin content of the serum before and after addisin are also being made, both in pernicious anemia and acholuric jaundice.

AGRANULOCYTIC ANGINA

In agranulocytic angina there has also been opportunity to study the effect of addisin in one patient.* A white male, aged 21, was admitted to the hospital January 15, 1933. There was a history of sore throat, beginning four days before admission. Two days later the temperature was 102. The throat became worse. He had one chill the night before admission, and was ex-

tremely prostrated. His temperature was 103, pulse 118, respirations 26. There were herpes on the lips and nose. Numerous superficial ulcers were seen on the gums and anterior pillars, and there was a larger ulcer on the lower half of the left tonsil. The glands at the angle of the jaw were enlarged and tender. The remainder of the physical examination was negative. Examination of the blood showed 6.7 million red cells, 115 per cent hemoglobin (Sahli), 1,400 leukocytes. A differential count showed only 7 per cent polymorphonuclear neutrophils and no other granulocytes. A diagnosis of agranulocytic angina was made.

On the evening of January 16th, the patient was given 30 units of addisin, and a remarkable leukocytic response followed, as shown in table 2. The counts were controlled with the supravital technic. In less than 24 hours there was an increase in the granulocytes, and soon myelocytes in appreciable quantity were found. Evidence of marked stimulation of the bone marrow is reflected in the differential counts and in the increase in the number of leukocytes. Rapid clinical improvement also accompanied this change in the blood. The temperature was normal at the end of two and one-half days following injection and has remained so.

Here again the result in a single case is so encouraging that an extensive trial of this form of treatment is indicated as soon as material, both clinical and therapeutic, is available.

The lack of an adequate supply of addisin of proved activity has prevented its trial in other blood diseases, such

*This case is being reported elsewhere in greater detail.

as secondary anemia, idiopathic hypochromic anemia, sickle cell anemia, the thrombopenic purpuras, the leukemias, et cetera.

2. Addisin may be recovered in a form suitable for intramuscular injection by concentration *in vacuo*, by dialysis and by conversion to an ethyl

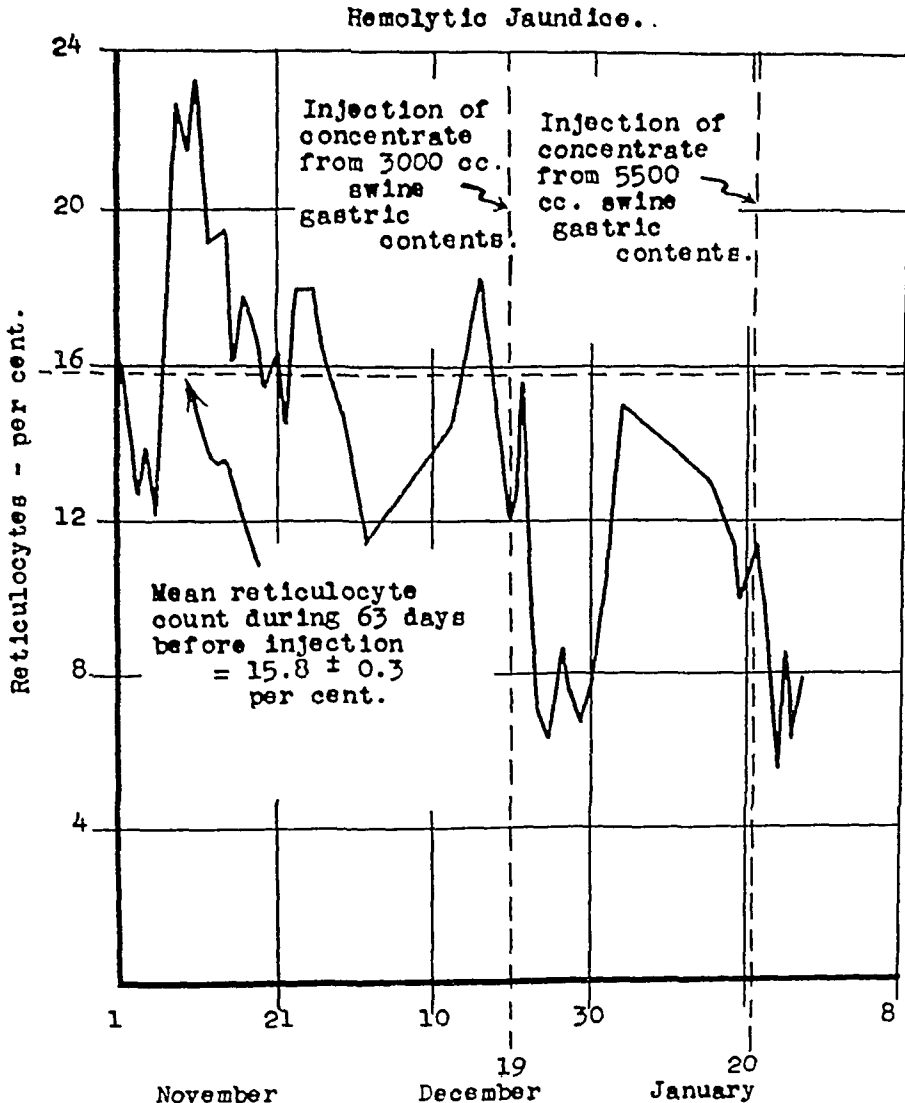


FIG. 5. The decrease in the percentage of reticulocytes following the injection of the concentrate of swine gastric contents.

CONCLUSIONS

1. An hemopoietic hormone (addisin) is a normal constituent of the gastric secretion of man, dogs, swine and cattle. It is probably widely distributed in the animal kingdom.

ester. A preparation for intravenous use has not yet been obtained.

3. A single large dose of addisin may be sufficient to induce a remission in pernicious anemia, and is more effective than repeated small doses.

4. There is evidence to suggest that

TABLE II
THE LEUKOCYTIC RESPONSE TO ADDISIN IN AGRANULOCYTIC ANGINA*

Date	Leuko- cytes	Lympho- cytes	Mono- cytes	Polymorpho- nuclears	Eosino- philes	Baso- philes	Myelo- cytes	Unclasi- fied
1-16	1,400	62.0	28.0	7.0	0.0	0.0	0.0	3.0
	(30 units of addisin—swine gastric contents—given 5 p.m., 1-16)							
1-17	1,600	39.0	39.0	12.0	5.0	0.0	3.0	2.0
1-18	2,700	41.0	28.0	23.0	3.0	0.0	2.0	3.0
1-19	2,300	48.0	18.0	30.0	0.0	0.0	1.0	3.0
	(Temperature normal since 6 a.m., 1-19)							
1-20	5,700	34.0	22.0	42.0	0.0	0.0	0.5	1.5
1-21	7,400	22.5	23.0	52.0	0.0	0.0	2.5	0.0
1-23	10,900	21.5	18.5	59.5	0.0	0.0	0.5	0.0

*The differential counts were controlled with supravital technic. The figures represent percentages. Blood for counts was taken daily in the forenoon.

the cause of erythremia may be a hypersecretion of addisin or a hypersusceptibility to stimulation by it on the part of the bone marrow.

5. The results of treatment of acholuric jaundice with addisin are sufficiently encouraging to warrant further trial. The possibility of establishing normal maturation of the red cells is suggested.

6. In a patient with agranulocytic angina, the leukocytic reaction and clinical improvement have been remarkably prompt. In this disease, it is possible that addisin may be curative.

7. Theoretical considerations indicate the possibility that addisin may play a significant rôle in other blood dyscrasias.

REFERENCES

- ¹MORRIS, R. S., SCHIFF, L., BURGER, G., and SHERMAN, J. E.: Specific hematopoietic hormone in normal gastric juice; preliminary note, *Jr. Am. Med. Assoc.*, 1932, xcvi, 1080-1081.—The hematopoietic response in pernicious anemia following the intramuscular injection of gastric juice, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 778-782.
- ²MORRIS, R. S., SCHIFF, L., FOULGER, J. H., RICH, M. L., and SHERMAN, J. E.: Observations on the hematopoietic hormone (addisin) in pernicious anemia, *Brit. Med. Jr.*, 1932, ii, 1050-1051.—Über die hämatopoetische Wirkung konzentrierten Magensaftes (Addisin) bei perniziöser Anämie, *Münch. med. Wchnschr.*, 1932, lxxix, 2074-2075.—Treatment of pernicious anemia; effect of a single injection of concentrated gastric juice (addisin), *Jr. Am. Med. Assoc.*, 1933, c, 171-173.
- ³CASTLE, W. B., HEATH, C. W., and STRAUSS, M. B.: Observations on etiologic relationship of achylia gastrica to pernicious anemia; biologic assay of gastric secretion of patients with pernicious anemia having free hydrochloric acid and that of patients without anemia or with hypochromic anemia having no free hydrochloric acid, and of the rôle of intestinal impermeability to hematopoietic substances in pernicious anemia, *Am. Jr. Med. Sci.*, 1931, clxxxii, 741-764.
- ⁴WILKINSON, J. F., and KLEIN, L.: Active principle in hog's stomach effective in pernicious anemia, *Lancet*, 1932, i, 719-721.

- ⁵WILLIAMS, H. A., and VANDER VEER, J. B.: Demonstration of anti-anemic factor in bovine gastric juice, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxix, 858-859.
- ⁶WILKINSON, J. F.: Discussion on the value of liver in treatment, *Proc. Roy. Soc. Med.*, 1931, xxiv (part 2), 948-951.
- ⁷CONNER, H. M.: Increase of reticulated erythrocytes in pernicious anemia following intramuscular injection of gastric juice, *Proc. Staff Meet., Mayo Clinic*, 1932, vii, 213-216.
- ⁸MORRIS, R. S., SCHIFF, L., and FOULGER, M.: Erythremia (polycythemia vera)—theory regarding etiology, *Jr. Med.*, 1932, xiii, 318-319.
- ⁹FOULGER, J. H., BURGER, G. N., MORRIS, R. S., and SCHIFF, L.: Preliminary studies of methods of concentration of the hemopoietic substance in gastric juice, *Jr. Med.*, 1933, xiv, 90.

Amebic Invasion of Lymphoid Tissue and Its Probable Clinical Significance*

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IN 1922, Ely, Reed and Wyckoff,¹ and Kofoid and Swezy² announced the finding of *Endameba histolytica* in the lesions of arthritis deformans. In this same year Kofoid, Boyers and Swezy³ described the presence of the amebae in the lymph nodes in cases of Hodgkin's disease. A new conception of the clinical picture of chronic amebiasis was developed as a result of these findings, and is described in the papers of Boyers, Kofoid and Swezy⁴ in 1925, and of Craig⁵ in 1927. The former authors, especially, stressed the multiplicity of symptoms due to chronic amebiasis and felt that the patients suffer from a true systemic infection with amebae, which they believed to be present in many sites in the body not previously considered as likely to be involved. Fatiguability, defective memory, loss of energy, nervousness and headache, are ascribed to the effects of chronic amebiasis on the nervous system. Digestive symptoms which suggest disordered function or even organic disease of the stomach or liver; constipation alternating with brief periods of diarrhea; cough, with or without bloody sputum; rapid pulse; defective vision, with or without iritis,

were also included as a part of the clinical picture. According to these authors, patients with chronic amebiasis might or might not show such gross lesions as abscess of the liver, lung, brain, skin ulcers, etc., as a cause for these widespread symptoms.

To explain the presence of amebae in places outside the colon, as, for instance, the liver, lungs, brain, spleen, bone marrow and lymph nodes, the conception of "systemic infection" had been previously offered by Kofoid, Boyers and Swezy,⁶ who asserted that: "From its portal of entry through the epithelium of the colon into the submucosa, *Endameba dysenteriac* tends to spread in the margins of ulcers of the colon into capillaries and smaller veins, and thence may make its way into the capillary net of the liver, through the heart to the capillary net of the lung, and thence into the systemic circulation." This new conception of chronic amebiasis stimulated a new interest in these diseases and led to more detailed pathological studies of amebic lesions, the findings of which have been published in papers during the past several years.

The present paper will present an account of the pathology of amebic lesions resulting from researches on the cultivation of *Endameba histolytica*

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in kittens in 1924 and 1925,⁷ and also notes of certain other studies carried out in collaboration with Dr. C. E. Forkner in Boston on a number of persons with Hodgkin's disease. The latter work was supervised by Dr. George R. Minot, of the Collis P. Huntington Memorial Hospital, and by the late Dr. Francis W. Peabody, director of the Thorndike Memorial Laboratory of the Boston City Hospital. In the discussion it will be shown that the results of these studies may provide a pathological basis for the clinical concept of chronic amebiasis.

PATHOLOGY OF AMEBIC LESIONS

Prior to the year 1891, much confusion existed among pathologists concerning the lesions found at autopsy in the so-called "follicular form" and in the "diphtheritic form" of dysenteries. In 1891, Councilman and Lafleur⁸ first accurately described the pathology of amebic lesions and established the differentiation between colitis of amebic origin and that of bacterial origin. By extensive review of the literature they showed that many of the cases of "follicular" and "diphtheritic" colitis, as previously described by American, English, French and German physicians in the tropical countries, were probably instances of amebic infection.

The work of Councilman and Lafleur was confirmed and amplified by that of other investigators, Rogers,⁹ Kuenen,¹⁰ Viereck,¹¹ and Woolley and Musgrave.¹² More recent investigators have studied the lesions in the intestines and liver of kittens experimentally infected with these parasitic amebae. Their studies revealed the identity of

the gross and microscopic amebic lesions in kittens with those in man. Furthermore, the finer pathological details of the very early lesions of amebiasis were more clearly described. We now know, as a result of these later studies by Dopter,¹³ Jürgens,¹⁴ Wenyon,¹⁵ Dale and Dobell,¹⁶ Sellards and Theiler,¹⁷ Boeck and Drbohlav,⁷ Rees,¹⁸ and Martin,¹⁹ that in experimental amebiasis in kittens, as in human amebiasis, there occurs not only an erosion-ulceration of the mucosa, often with the formation of a diphtheritic membrane, that may later invade the deeper coats of the colon, appendix and terminal ileum, but also invasion and destruction of solitary lymph follicles. We shall now briefly consider the microscopic appearance of the intestinal lesions found in amebiasis.

Intestinal Lesions. In stained sections of tissues of the colon, amebae may be found upon the surface of the epithelium (figure 1) and less frequently in the glandular crypts. They appear to secrete a toxic and proteolytic substance or substances that cause a cytolytic and liquefying necrosis of the tissues they invade. They first produce an erosion-lesion of the surface epithelium and sometimes form, with the aid of a secondary bacterial invasion, a diphtheritic membrane composed of fibrin, mucus, cellular remains, bacteria, and amebae (figure 1). This membrane was noted in the early observations of Finger (1849), Lyons (1856), Parkes (1860), Woodward (1880), and Maclean (1886), cited by Councilman and Lafleur.⁸

Following the destruction of the epithelium by the formation of erosion-ulcers, the amebae may continue to de-

stroy simultaneously both the interstitial tissue of the tunica propria and the epithelial covering of the glands. They may often, however, be seen passing into and down the lymphatic channels of the tunica propria into larger lymphatics in the submucosa. There they seem to be arrested in their progress,

bacterial invasion of variable amount may occur in many of the larger ulcers and the deeper erosion-ulcer lesions. The results of this complication are marked polymorphonuclear infiltration and a purulent exudate.

Liver, Lung and Brain Abscesses. With the formation of deep ulcers in



FIG. 1. Erosion-ulceration by amebae, with formation of diphtheritic membrane. $\times 150$.

creating a localized area of necrosis and forming abscesses. As this area grows the overlying mucosa may slough with the production of a large deep ulcer (figure 2). The amebae in the bottom of the glands cause necrosis of the adjacent epithelial cells of the crypt and invade the mucosa above the muscularis mucosae; later a larger ulcer develops from the sloughing of the mucosa above the lesion. Secondary

the submucosa, the amebae may find their way into the blood capillaries and may thus be carried by the portal circulation to the liver. Here, in some cases, a hepatitis occurs which may progress, by proteolytic and liquefying necrosis of the liver parenchyma, and result in single or multiple amebic abscesses. A pulmonary abscess may be produced from this focus in the liver most frequently by direct extension

through the diaphragm and occasionally by blood stream invasion. In rare cases further blood stream invasion has caused an embolic brain abscess or an abscess of the spleen. These instances, however, have nearly always been associated with an older abscess of either the liver or lung and gen-

tissues are also important because of their probable relationship to the symptoms present in cases of chronic amebiasis.

Lesions in Lymph Follicles. Opportunities of observing several progressive stages in the early invasion, as well as the gradual and ultimate de-



FIG. 2. Deep submucosal amebic ulcer with complete destruction of intestinal mucosa.
x 75.

erally with a previous amebic colitis. This, in a general way, characterizes the manner and progress of amebic infection in the intestine, liver and lungs, with the exception of lesions in the lymphoid tissues. The pathology of the lesions in lymphoid tissues has not been studied as extensively as that of the ulcerative lesions of the intestine, although lesions in the lymphoid

struction of the lymph follicles, were afforded by lesions occurring in Peyer's patches of the terminal ileum of five kittens experimentally infected with *Endameba histolytica*. The amebae showed an apparent selective action in attacking the follicles, as was evident from an initial necrosis of the epithelium covering the tip of the solitary follicle. The adjacent epithelium

of the intestinal mucus glands was not affected (figures 3 and 4). Following the destruction of the epithelium over the follicle, the amebae moved down into the body of the follicle, and a sinus tract was formed. The lymphoid cells of the follicle and the interstitial cells

tered polymorphonuclears, large mononuclear cells, and a proliferation of connective tissue elements, attempting to wall off the lesion. In the center of the gland there was progressive destruction of the lymph cells by the amebae, resulting in much cellular de-



FIG. 3. Very early amebic abscess in solitary follicle, with destruction of epithelium over tip of the follicle, and downward migration of amebae—adjacent epithelium normal. $\times 100$.

of the reticulum underwent necrosis, the nuclei becoming pyknotic and the cytoplasm undergoing gradual dissolution or liquefaction (figure 5). There was practically no evidence of any cellular reaction to the infection in the early stages of the invasion, but later stages showed an infiltration of the submucosa at the outer limits of each follicle, with plasma cells chiefly, scat-

tritus. The amebae, as they multiplied and formed a localized abscess, appeared as large cells within a nest of lymphoid cells (figures 6 and 7). The abscess thus produced continued to grow until the whole follicle was destroyed. Later, the mucosa overlying the abscess in the submucosa may, in some cases, slough off and produce a large deep ulcer (figure 8). There

was no evidence of bacterial invasion of the follicles in the early stages of the amebic invasion.

The follicles in the colon also showed early invasion by amebae. This condition, too, was noted by pathologists studying lesions from the human colon. Such an invasion of lymphoid tissue

lymphoid follicles of the colon and terminal ileum in human cases. Although these early investigators felt that the disease often began in these structures, Councilman and Lafleur considered the amebic invasion of the follicles a passive action. Somewhat later Kuenen¹⁰ reported the death of a

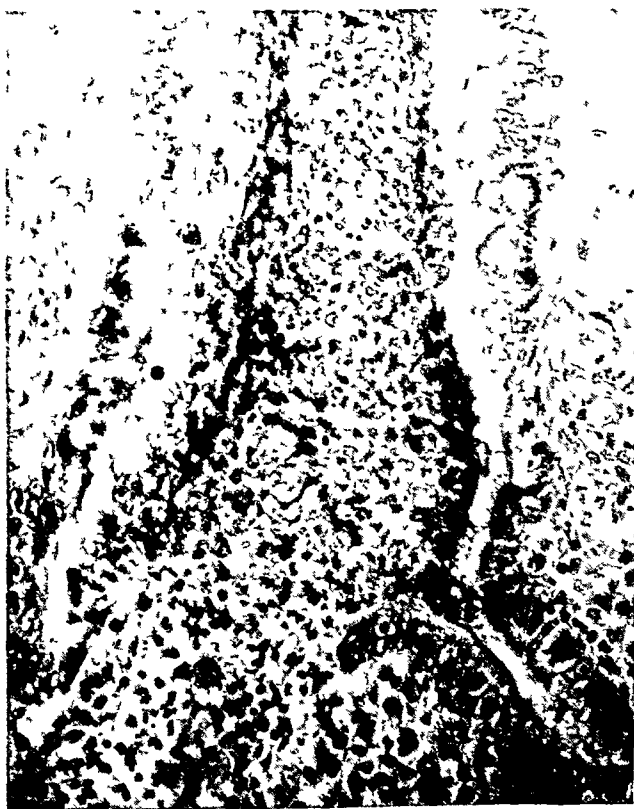


FIG 4 Same as figure 3, except higher magnification, to show amebae in lymph follicle and normal adjacent epithelium. $\times 200$.

may, however, go on simultaneously with the erosion destruction of the mucosa adjacent to the follicle or elsewhere, depending upon the location of the amebic invasion (figure 9).

The observations of Lyons (1856), Parkes (1860), Woodward (1880), and Maclean (1886), cited by Councilman and Lafleur, also showed abscesses or ulcers occurring first in the

patient due to peritonitis from a perforation of the ileum by amebae invading a Peyer's patch. This same patient also had typhoid fever, so the cause of the perforation may have been of typhoid origin, the amebae being present in the lesion and passing through into the abdomen. Very recently Hegner, Johnson and Stabler²⁰ reported amebic invasion of lymph follicles in

an appendix removed at operation from a patient in whose stools *Endameba histolytica* had been previously found.

The very recent studies made by various investigators of lesions of the lymphoid follicles occurring in kittens and monkeys experimentally infected

vessels and produce submucous abscesses in the follicles." He felt that the follicular abscesses were of bacterial origin, amebae wandering into and around them after death of the kitten. Hegner, Johnson and Stabler, who studied experimental amebic lesions in monkeys, were of the opinion



FIG. 5. Amebic abscess in lymph follicle, showing sinus tract to lumen of intestine—no ulceration of adjacent epithelium. $\times 50$.

with *Endameba histolytica* are not in agreement as to whether such lesions should be attributed to amebic or to bacterial action.

Iiyeda²¹ found no amebae in follicular ulcers, and thought that the lesions were due to bacterial invasion. Ratcliffe²² believed that: "The apparent rôle of the amebae is superficial destruction of the mucosa which allows pyogenic bacteria to invade the lymph

that the follicular abscesses were of bacterial origin because they found no amebae in them. On the other hand, Dopter, Jürgens, Martin and the author have recorded observations in which the amebae were found in the abscesses of the lymph follicles. We may conclude, therefore, that follicular abscesses may be of either bacterial or amebic origin. Abscesses of both types may occur in the same subject. Of

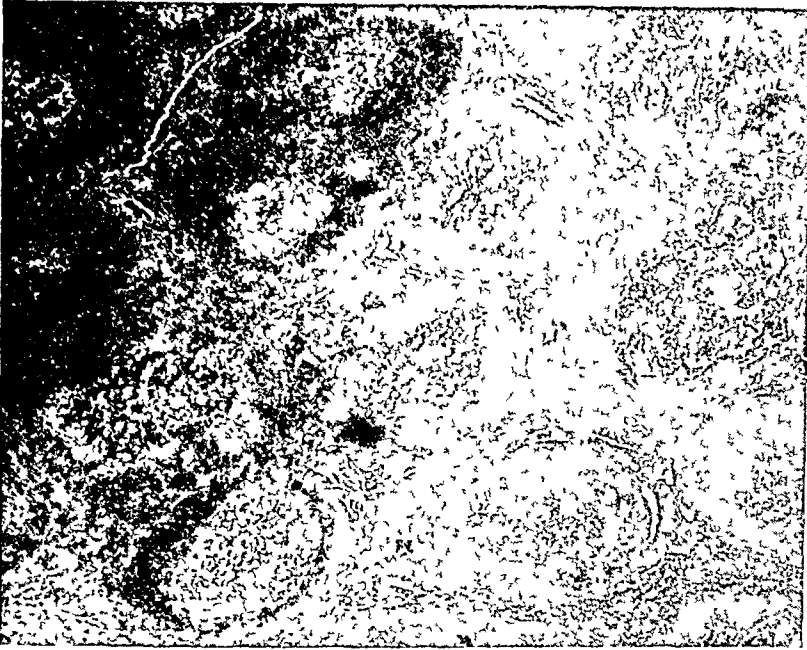


FIG. 6. Peyer's Patch, frontal section, showing nest of amebae in each follicle. $\times 30$.



FIG. 7. Amebic follicular abscess, from figure 6, higher magnification. $\times 75$.

such a nature were some of the cases reported in early writings on "follicular" colitis. It may be that the very early lesions as reported by Jürgens and the author were not observed by Hiyeda, Ratcliffe, nor by Hegner and his associates.

writer's observations and those of Jürgens indicate that these glands are very early attacked by the amebae, even before the adjacent epithelium is damaged, and long before there is any evidence of bacterial invasion such as Ratcliffe maintained. It is also signifi-



FIG. 8. Large sloughing follicular abscess. x 75.

Jürgens was the earliest investigator to note that in kittens the amebae seemed to invade the lymph follicles first while the adjacent intestinal epithelium remained intact and apparently healthy. Although Martin also observed amebic abscesses in the follicles, he did not feel that these structures were predisposed to the attack of *Endameba histolytica*. He did not, however, observe early stages in the invasion of these glands. The present

cant that the appendiceal infection with *Endameba histolytica*, reported by Hegner, Johnson and Stabler, showed, as the only evidence of microscopic damage, two small early amebic ulcers in the lymph follicles.

To summarize, the pathology of amebic lesions indicates that there are two distinct, fundamental lesions produced by these parasites; first, an early erosion-ulcer which is the result of the invasion and destruction of epithelial

tissue of the intestine (this is also true when other epithelial structures are attacked); second, an abscess which is produced in solitary lymph follicles, the liver, lung, brain and spleen. There is considerable pathological evidence

These glands contained certain cells which were interpreted as *Endameba histolytica* by the authors. Later they reported that amebae were found in the stools of 18 out of 20 cases of Hodgkin's disease studied by them.



FIG. 9. Solitary follicular amebic abscess, with erosion-ulceration and diphtheritic membrane above. $\times 75$.

that the amebae may attack the lymph follicles of the colon, appendix and terminal ileum before producing much or any damage to the adjacent epithelium.

AMEBIASIS AND HODGKIN'S DISEASE

Kofoed, Boyers and Swezy,⁸ in 1922, reported on several cases of Hodgkin's disease confirmed by pathological examination of excised lymph glands.

Dr. C. L. Forkner and the author, while in Boston, studied a number of cases of Hodgkin's disease from two aspects. Dr. Forkner was interested in the diagnosis of diseases, such as Hodgkin's and malignancy, by glandular puncture. The affected glands were punctured with a needle in the lumen of which was a coarse dental broach. The rotation of this broach and its subsequent withdrawal brought away cellular material which could then be

stained with supravital dyes and studied in the warm chamber. The report of this part of the study has been published by Dr. Forkner.^{23,24}

The author's part in this investigation was the search for *Endameba histolytica* in the lymph node material. Culture media were inoculated to grow any amebae that might be present; and hematoxylin-stained smears were studied microscopically. The stools from many of these patients were also examined for *Endameba histolytica*. Some of the cases studied were not, however, included in the published reports of Dr. Forkner.

All the cases studied had had definite pathological diagnoses which, with few exceptions, coincided with the results obtained from gland puncture. The author collaborated in a study of fifteen cases of lymphoblastoma, of which nine were diagnosed as Hodgkin's disease; three as lymphoblastoma of the rapidly growing type; and two as lymphoblastoma of the leukemic type. In none of the cases of lymphoblastoma reported by Forkner, nor in any of the additional cases studied and not reported, was *Endameba histolytica* ever observed either among the living cells stained with vital dyes, or in the stained pathological sections of the glands. Biopsy material obtained from the nine cases of Hodgkin's disease was inoculated in culture media, but these cultures also proved negative for amebae.

The stool examinations of these patients revealed that *Endameba histolytica* was present in the stools of but one of these cases. *Endameba coli* was also present in this case. Of the remaining eight cases, *Endameba coli* occurred in one case, *Endolimax nana* in one case, and *Giardia lamblia* in one

case; the other five cases were negative for intestinal protozoa. Three stool examinations were made in one of these cases; and six stool examinations in each of the other eight cases. The results of the stool examinations were in marked contrast with those obtained by Kofoed, Boyers and Swezy⁶ who found *Endameba histolytica* in the stools of eighteen out of twenty patients having Hodgkin's disease.

To summarize this investigation of the nine cases of Hodgkin's disease: amebae were absent in the stained pathological sections, in the living cells obtained by gland puncture, in this same cellular material stained with hematoxylin, and in culture media inoculated with this cellular material.

DISCUSSION

The clinical concept of chronic amebiasis held by Boyers, Kofoed and Swezy and others has not, for several reasons, met with general acceptance by physicians and pathologists. Their attempt to ascribe an etiological rôle to chronic amebiasis in symptom complexes characteristic of what is usually termed neuresthenia, and in such disease processes as iritis, neuritis, arthritis deformans and Hodgkin's disease could only be justified by proof of the presence of *Endameba histolytica* in the tissues of such cases.

Pathologists have failed to identify any of the cells in lesions of arthritis deformans as identical with *Endameba histolytica*. Likewise, the progressive pathology of these destructive lesions of bone is not in any way suggestive of amebic invasion, since no liquefying necrosis occurs with local abscess formation, such as is found in amebae-infested tissues. Further, the forma-

tion of bony lipping and spurs is not consistent with amebic pathology.

The presence of amebae in the enlarged lymph nodes of Hodgkin's disease has not been confirmed by other pathologists who have made a careful study of this disease. The author's investigations, as well as those of Jürgens, Martin and others, have shown that when amebae invade lymphoid follicles abscess formation results and that in such lesions amebae are easily detected. Abscess formation is very unusual in the lymph glands of Hodgkin's disease if it occurs at all. Moreover the cells in Hodgkin's glands, which Kofoid, Boyers and Swezy believed to be amebae, were difficult to find. The author's investigations on nine cases of Hodgkin's disease, together with those of Forkner and more recently those of Twort²⁵ in 1930, covering 61 cases of Hodgkin's disease, have failed to show that *Endameba histolytica* is present in the enlarged glands or in cultures inoculated with material from these glands.

All previous investigators have found little evidence of generalized systemic invasion with *Endameba histolytica*. Liver abscess, it is true, has for about 40 years been assumed to be due to ameba reaching the liver through the blood stream. However, even in India where this complication is most frequently seen, it occurs in only 20 per cent of the cases of amebic colitis. The liver is usually an efficient filter which prevents amebae from entering the blood stream. The fact that even a small amount of bile in cultures is fatal to amebae may account in part for the effective defensive rôle of the liver. Councilman and Lafleur,⁸ Manson-Bahr,²⁶ Clark²⁷ and others have shown

that when lung abscess occurs it is more usually as a result of direct extension from a liver abscess than by invasion of the lung by amebae carried in the circulating blood. Amebic abscesses of the brain, spleen and kidneys, which are evidence of invasion of the systemic circulation, are quite rare. Therefore, to assume that systemic amebic invasion occurs with such frequency as to be accountable for such relatively common diseases as arthritis deformans, Hodgkin's disease, iritis, etc. is contrary to all previous knowledge of the pathology of the disease.

Because, then, of the lack of confirmation of their findings and because of the inherent improbability of their conception of systemic invasion, physicians and pathologists generally have not accepted the views of Boyers, Kofoid, and Swezy.

Another conception of the relationship of general constitutional conditions to chronic amebiasis was brought forward by Barrow. He first suggested that chronic amebiasis and arthritis may be related, as Ely, Reed and Wyckoff later stated, but he held that the relationship was due to the probable presence of small lesions in the intestine that permitted the absorption of toxins, and not to the presence of amebae in the bone marrow in cases of arthritis deformans.

This particular conception of chronic amebiasis finds a definite pathological basis in the studies of the lesions of the solitary lymph follicles. All infections of *Endameba histolytica* must be considered potentially dangerous to health even in the so-called carrier cases of chronic amebiasis, as has been known for a long time. For the reasons given above, it is hardly probable

that in such chronic cases the amebae reach the bone marrow or lymph glands. They may, however, cause slight erosion-lesions of the intestinal mucosa, and may invade the solitary lymph follicles, causing abscesses such as have been previously described. These small lesions, which would not be detectable in the sigmoidoscope, represent definite portals of entry into the lymphatic system for the absorption of toxins from the colon. Hence each lesion is a focus of infection. The toxins may be liberated either by the amebae, or by the bacteria in these lesions. The toxins from the bacteria may be the more important etiological factors in the production of inferior health and chronic disease in individuals infested with *Endameba histolytica*.

The clinical application of these pathological observations is clear and indicates that all patients who are in poor health and underweight, those with nervous and physical exhaustion, and those who may be subject to recurrent attacks of arthritis and other diseases for which focal infections are

believed to be partly responsible, should be thoroughly examined for *Endameba histolytica*, just as they are examined for infected tonsils, abscessed teeth and other foci. If an amebic infection is discovered it should be eradicated by thorough treatment. Too much in the general improvement of the patient should not be expected, in view of the fact that there are most likely multiple factors at work.

To summarize, it has been shown that there are two fundamental kinds of amebic lesions: first, erosion-ulcers of the epithelium which may become deep and undermining in character, often secondarily invaded by bacteria; second, a localized abscess in lymph follicles, liver, lung, brain and spleen. Further investigations on cases of Hodgkin's disease have failed to show any amebae present in the enlarged lymph nodes. It is suggested that the small erosion-ulcers of the epithelium, and especially the localized abscesses seen in the solitary lymph follicles, provide a pathological basis for the clinical conception of chronic amebiasis.

REFERENCES

- ¹ELY, L. W., REED, A. C., and WYCKOFF, H. A.: The ameba as the cause of the second great type of chronic arthritis, Calif. State Jr. Med., 1922, lix, 59.
- ²KOFOID, C. A., and SWEZY, O.: On the occurrence of *Endameba dysenteriae* in bone lesions in arthritis deformans, Calif. State Jr. Med., 1922, lix, 59.
- ³KOFOID, C. A., BOYERS, L. M., and SWEZY, O.: Occurrence of *Endameba dysenteriae* in the lesions of Hodgkin's disease, Jr. Am. Med. Assoc., 1922, lxxviii, 1604.
- ⁴BOYERS, L. M., KOFOID, C. A., and SWEZY, O.: Chronic human amebiasis: a review of the diagnosis and treatment on the basis of encystment in the liver area, Jr. Am. Med. Assoc., 1925, lxxxv, 1441.
- ⁵CRAIG, C. F.: The symptomatology of infection with *Endameba histolytica* in carriers, Jr. Am. Med. Assoc., 1927, lxxxviii, 19.
- ⁶KOFOID, C. A., BOYERS, L. M., and SWEZY, O.: Systemic infections by *Endameba dysenteriae*, Proc. Internat. Conference on Health Problems in Tropical America, United Fruit Company (Boston), 1924, 381.
- ⁷BOECK, W. C., and DRBOHLAV, J.: The cultivation of *Endameba histolytica*, Am. Jr. Hyg., 1925, v, 371.
- ⁸COUNCILMAN, W. T., and LAFLEUR, H. A.: Amebic dysentery, Johns Hopkins Hosp. Rep., 1891, ii, 395.

- ⁹ROGERS, L.: Further work on amebic dysentery in India, *Brit. Med. Jr.*, 1903, i, 1315.
- ¹⁰KUENEN, W. A.: Die Pathologische Anatomie der Amoebiasis verglichen mit anderen Formen von Dysenteriae, *Arch. f. Schiffs- u. Tropen-Hyg.*, 1909, xiii, 435.
- ¹¹VIERECK, H.: Studien über die in den Tropen erworbene Dysenterie, *Arch. f. Schiffs- u. Tropen-Hyg.*, 1907, xi, 1.
- ¹²WOOLLEY, P. G., and MUSGRAVE, W. E.: The pathology of intestinal amebiasis, *Jr. Am. Med. Assoc.*, 1905, xlv, 1371.
- ¹³DOPTER, C.: Sur quelques points relatifs à l'action pathogène de l'amibe dysentérique, *Ann. de l'Inst. Pasteur*, 1905, xix, 417.
- ¹⁴JÜRGENS: Die Amöben-Enteritis und ihre Beziehungen zur Dysenterie, *Ztschr. f. exper. Path. u. Therap.*, 1907, iv, 769.
- ¹⁵WENYON, C. M.: Experimental amebic dysentery and liver abscess in cats, *London School of Tropical Medicine*, 1912-1913, ii, 27.
- ¹⁶DALE, H. H., and DOBELL, C.: Experiments on the therapeutics of amebic dysentery, *Jr. Pharmacol. and Exper. Therap.*, 1917, x, 399.
- ¹⁷SELLARDS, A. W., and THEILER, M.: Investigations concerning amebic dysentery, *Am. Jr. Trop. Med.*, 1924, iv, 309.
- ¹⁸REES, C. W.: Pathogenesis of intestinal amebiasis in kittens, *Arch. Path.*, 1929, vii, 1.
- ¹⁹MARTIN, D. L.: The lesions in experimental amebic dysentery, *Arch. Path.*, 1930, x, 349-385, 531-579.
- ²⁰HEGNER, R., JOHNSON, C. M., and STABLER, R. M.: Host-parasite relations in experimental amebiasis in monkeys in Panama, *Am. Jr. Hyg.*, 1932, xii, 394.
- ²¹HIYEDA, K.: Pathological-anatomical studies on experimental amebiasis in kittens, *Am. Jr. Hyg.*, 1930, xii, 401.
- ²²RATCLIFFE, H. L.: A comparative study of amebiasis in man, monkeys and cats, with special reference to the formation of the early lesions, *Am. Jr. Hyg.*, 1931, xiv, 337.
- ²³FORKNER, C. L.: Material from lymph nodes of man. I. Method to obtain material by puncture of lymph nodes for study with supravital and fixed stains, *Arch. Int. Med.*, 1927, xl, 532.
- ²⁴FORKNER, C. L.: Material from lymph nodes of man. II. Studies on living and fixed cells withdrawn from lymph nodes of man, *Arch. Int. Med.*, 1927, xi, 647.
- ²⁵TWORT, C. C.: Etiology of lymphadenoma; summary of six years' researches, *Jr. Path. and Bact.*, 1930, xxxiii, 539.
- ²⁶MANSON-BAHR, P. H.: *Manson's tropical diseases*, 9 Ed., 1929, William Wood, New York.
- ²⁷CLARK, H. C.: The distribution and complications of amebic lesions found in 186 postmortem examinations, *Am. Jr. Trop. Med.*, 1925, v, 157.

Variations in the Volume and in the Acid Content of Gastric Secretion of Normal Individuals Following Stimulation by Histamine*†

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DURING the last few years the analysis of gastric contents obtained after stimulation by histamine has come into general use.

The work of Bloomfield and Poland^{1,2} on the acidity of gastric juice following histamine stimulation has shown that the volume and acidity rapidly increase, the maximum being reached in 20 to 30 minutes after injection, after which time the volumes diminish, while the acidity maintains its high level throughout the test of an hour's duration. They found a constancy of response of volume and acid after giving repeated doses of the same amount of histamine to a given individual.

Gompertz and Cohen³ have shown that as little as 0.25 mg. of histamine hydrochloride will give a gastric secretory response, and that in using larger doses (0.5 mg., 0.75 mg., 1.0 mg.) a greater response is usually obtained, but that the results are not mathematically proportional to the size of the dose.

Kinsella,⁴ after reviewing the literature concerning the acidity at the cardiac and pyloric ends of the stomach, reports that he finds the gastric contents usually more acid at the cardiac than at the pyloric end if saliva is excluded.

The gastric secretion after stimulation by histamine has been studied in two healthy men aged 28 and 32 years. In aspirating the gastric secretion the Rehfuess tube was used, the 60 cm. mark being kept at the incisor teeth. Continuous aspiration of the gastric secretion was performed at a negative pressure of 15 to 20 cm. of mercury, maintained by a water driven suction pump. A 15 minute fasting sample (fasting contents and any gastric secretion over 15 minutes' time) was obtained; then histamine (ergamine phosphate) was administered subcutaneously, 0.1 mg. per 10 kilograms of body weight, and the subsequent gastric secretion obtained was divided into six 10 minute samples. The volume of each sample was measured, and free and total acidity of each sample was determined using dimethylamino-azobenzol (Topfer's reagent) and phenolphthalein as indicators, the acidity being expressed in terms of 0.1 normal

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acid per 100 c.c. of gastric juice. The study was carried on over a period of eight months, 16 analyses being done on one subject and seven on the other. In each of the charts the solid lines indicate the response to 0.1 mg. histamine per 10 kilograms of body weight; the broken lines to half this dose; and the dotted lines to one-fourth the first mentioned dose. All of the analyses were done by the same two individuals, thereby tending to minimize errors due to variations of technic.

Charts 1, 2, and 3 on subject F. E. show: (1) that the maximum acidity and the maximum volume per 10 minute period were always reached in the 10 to 20 minute or in the 20 to 30 minute samples, usually in the former; (2) that after the maximum acid secretion is reached, the acid rapidly diminishes, tending to approach the fasting level at the end of an hour after the administration of histamine, while there is less diminution noted in the amount of secretion per 10 minute period; (3) that a close relationship exists between the free and total acid;

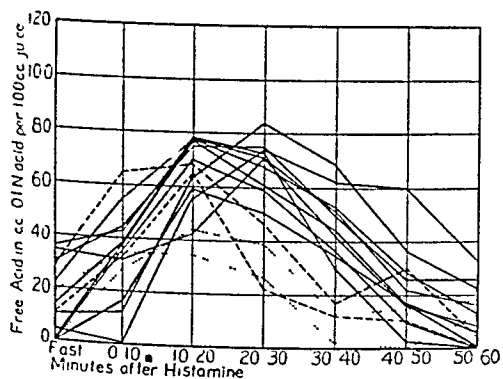


CHART I. F. E. Free Acidity Curves.
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.
Broken lines = 0.05 mg. histamine per 10 kilograms body weight.
Dotted lines = 0.025 mg. histamine per 10 kilograms body weight.

(4) the maximum free acid varied from 58 to 86, the maximum total acid varied from 75 to 96, and the maxi-

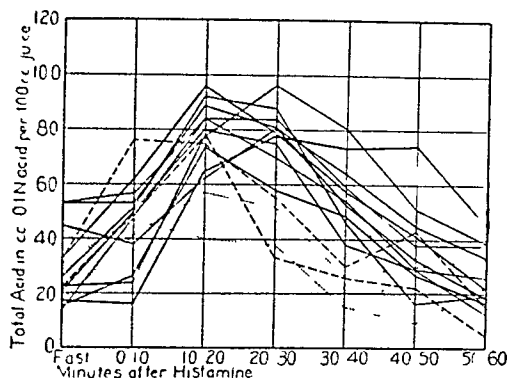


CHART II. F. E. Total Acidity Curves.
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.
Broken lines = 0.05 mg. histamine per 10 kilograms body weight.
Dotted lines = 0.025 mg. histamine per 10 kilograms body weight.

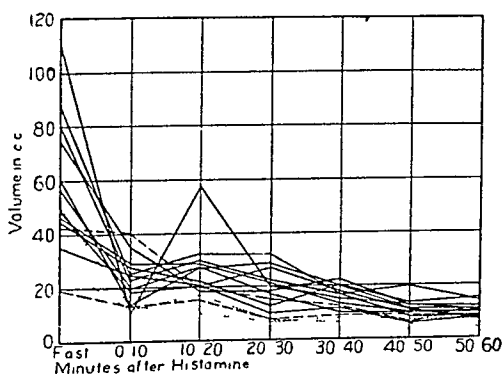


CHART III. F. E. Volume Curves.
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.
Broken lines = 0.05 mg. histamine per 10 kilograms body weight.
Dotted lines = 0.025 mg. histamine per 10 kilograms body weight.

imum volume for the 10 minute period varied from 21 to 33 c.c. except on one occasion when 56 c.c. were obtained; (5) one-half of the dose of histamine gave less volume of secretion but nearly as high an acid level as the full dose; (6) one-fourth of the dose of hista-

mine did not elicit the average full dose response in either volume or acid.

Charts 4, 5, and 6 on subject C.L.B. show (1) that the maximum acidity and the maximum volume per 10 min-

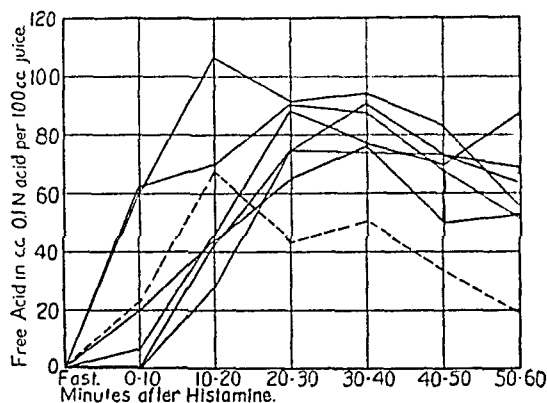


CHART IV. C. L. B. Free Acidity Curves.
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.
Broken line = 0.05 mg. histamine per 10 kilograms body weight.

ute period were always obtained by the end of 40 minutes after the injection of histamine, usually in the 20 to 30 minute or in the 30 to 40 minute samples; (2) that after the maximum acid secretion and the maximum volume per 10 minute period were reached there

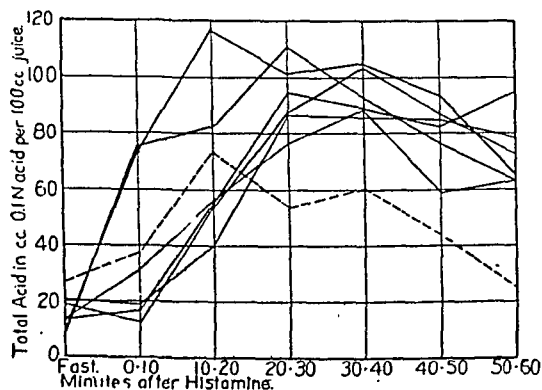


CHART V. C. L. B. Total Acidity Curves.
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.
Broken line = 0.05 mg. histamine per 10 kilograms body weight.

was a tendency for both acid and volume to diminish but not as rapidly as in subject F. E.; (3) that a close relationship exists between the free and total acid; (4) the maximum free acid varied from 75 to 106, the maximum total acid varied from 87 to 113, and the maximum volume per 10 minute period varied from 42 to 84 c.c.; (5) one-half of the dose of histamine did not elicit the average full dose response in either volume or acid.

Since continuous aspiration removes practically the entire secretion of the stomach it is possible to obtain from the results of these tests a quantitative measure of gastric secretory function. The influence of regurgitation of duodenal contents was probably of no significance in these tests since none of the samples was stained with bile. The amount of free or total acid, expressed as 0.1 normal acid, secreted during the hour test period is calculated in the following manner: the volume in c.c. of each 10 minute sample is multiplied by the amount of acid, in terms of 0.1 normal acid, per c.c. of that juice, and the sum of the values of each of the

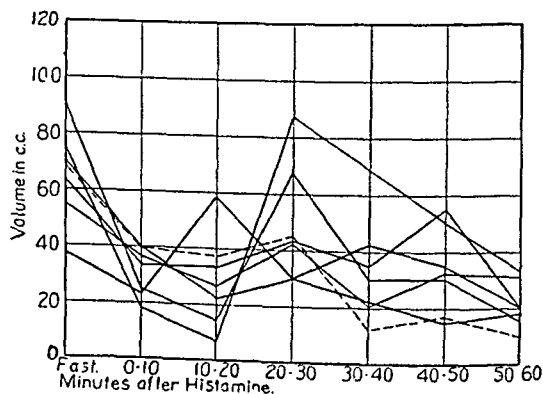


CHART VI. C. L. B. Volume Curves.
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.
Broken line = 0.05 mg. histamine per 10 kilograms body weight.

six samples gives the total acid secretion for the hour. Table 1 shows the volume and the quantity of free and total acid secretion in the hour following stimulation by histamine. A considerable variation of acid secretion in the same individual given the same dose of histamine on different days is shown by these figures.

samples usually had the greater free and total acidity. We believe that this experiment indicates that the tube at 60 cm. removes practically all of the gastric secretion and that the secretion obtained from the cardiac end of the stomach usually has a greater acidity than that removed from the pyloric end.

TABLE I

Subject	Date 1931	Histamine in Mg. per 10 Kilograms of Body Weight	Gastric Secretion Obtained in the Hour Following Histamine Stimulation		
			Volume in c.c.	Free acid as c.c. 0.1 N. acid	Total acid as c.c. 0.1 N. acid
F.E.	4-15	0.1	100	55	66
F.E.	4-20	0.1	140	70	82
F.E.	4-22	0.1	110	42	54
F.E.	4-27	0.1	107	61	71
F.E.	4-29	0.1	126	50	68
F.E.	5- 8	0.1	122	66	78
F.E.	5-11	0.1	110	37	53
F.E.	5-13	0.1	109	51	64
F.E.	5-18	0.1	81	39	49
F.E.	5-20	0.1	92	55	64
F.E.	11-20	0.05	104	49	61
F.E.	11-23	0.025	51	17	23
F.E.	11-27	0.025	56	13	19
F.E.	11-30	0.05	62	18	25
C.L.B.	4-13	0.1	219	138	159
C.L.B.	4-22	0.1	165	119	143
C.L.B.	4-24	0.1	189	153	174
C.L.B.	5-11	0.1	195	127	152
C.L.B.	5-20	0.1	188	105	123
C.L.B.	11-23	0.1	181	96	113
C.L.B.	11-25	0.05	160	65	83

Table 2 shows the results on subject F. E. when two Rehfuß tubes were used at the same time with simultaneous and continuous aspiration, the tip of one being 60 cm. and the other 72 cm. from the incisor teeth, these tube tips being found by X-ray examination to be in the cardiac and pyloric ends of the stomach respectively. It will be noted that almost all of the secretion was obtained from the tube in the cardiac end of the stomach and that these

Our studies show less constancy in both volume and acid secretion in the same individual after repeated doses of the same amount of histamine than was found by Bloomfield and Pollard. The gastric contents were usually more acid at the cardiac than at the pyloric end of the stomach. Smaller doses of histamine, while they elicit some gastric secretion, do not seem to be as satisfactory as a dose of 0.1 mg. per 10 kilograms of body weight.

TABLE II
ANALYSIS OF GASTRIC CONTENTS OF F.E. USING 2 REHFUSS TUBES, TIPS 60 AND 72 CM.
FROM INCISOR TEETH, 0.1 MG. HISTAMINE PER 10 KILOGRAMS BODY WEIGHT

Specimen	60 cm. tube			72 cm. tube		
	Volume in c.c.	Free acid	Total acid	Volume in c.c.	Free acid	Total acid
15' fasting	80	0	19	10	0	16
0'-10' after hist.	12	28	47	2	0	18
10'-20' " "	18	63	75	4	37	44
20'-30' " "	13	61	73	1	42	55
30'-40' " "	11	28	40	0	—	—
40'-50' " "	8	12	26	1	35	58
50'-60' " "	7	5	23	3	4	23

Specimen	60 cm. tube			72 cm. tube		
	Volume in c.c.	Free acid	Total acid	Volume in c.c.	Free acid	Total acid
15' fasting	24	14	23	7	5	17
0'-10' after hist.	20	21	33	3	10	19
10'-20' " "	30	70	86	1	33	47
20'-30' " "	11	58	67	5	44	58
30'-40' " "	8	26	40	1	25	42
40'-50' " "	8	2	18	2	21	37
50'-60' " "	11	2	16	6	0	14

SUMMARY

1. A study of the variations in the volume and acid content of gastric secretion of two normal individuals, following stimulation by histamine (ergamine phosphate), is presented.
2. A maximum in volume and in acidity of the gastric secretion is obtained, on the average, about 30 minutes after the administration of histamine.

3. There are distinct variations in the volume and in the acidity of the gastric secretion of the same individual given the same amount of histamine on different days.
4. When gastric secretion is removed from the pyloric and cardiac ends of the stomach at the same time, the acid content of the secretion obtained at the cardiac end is usually greater.

BIBLIOGRAPHY

¹BLOOMFIELD, A. L., and POLLAND, W. S.: The diagnostic value of studies of gastric secretion, Jr. Am. Med. Assoc., 1929, xcii, 1508-1513.

²POLLAND, W. S.: Stimulation of gastric pepsin by histamine, Jr. Clin. Invest., 1932, xi, 449-454.

³GOMPertz, L. M., and COHEN, W.: Further studies on the action of histamine on human gastric secretion, Tr. Am. Gastro-Enterol. Assoc., 1929, xxxi, 28-37.

⁴KINSELLA, V. J.: Regional analysis of the stomach contents; a comparison of the cardiac and pyloric curves, Med. Jr. Australia, 1928, ii, 430-433.

Orthostatic Albuminuria

A Comparison with Other Types of Albuminuria*†

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AFTER rather completely reviewing the extensive literature of the last twenty years on orthostatic albuminuria, it is apparent that many clinical impressions have been accepted as fact without proper critical study. Few authors have presented sufficient data on carefully studied series of cases to lend weight to their conclusions.

In an effort to obtain some accurate information about orthostatic albuminuria, its effect on the patient's health, the relation it bears to glomerulonephritis, the type of patient affected, and if possible its etiology, the records of 185 patients seen at The Mayo Clinic over a period of approximately ten years were carefully analyzed. The results were tabulated at length, and the tables made are summarized in table 1. The cases studied have been divided into four groups: (1) orthostatic albuminuria; (2) albuminuria with an orthostatic response; (3) latent glomerulonephritis, and (4) chronic glomerulonephritis.

The diagnostic criteria for inclusion of cases in the first group have been the occurrence of albumin in the urine when the patient was in the erect position, whereas a specimen excreted while the patient was lying down, or the night specimen, must have been entirely free from even traces of albumin by the usual method of detection. It is possible that this rule has excluded certain cases of orthostatic albuminuria from our first group, since, in genuine cases of this sort, the albuminuria has been demonstrated to persist a short time after the patient has lain down. The sediment in such cases is usually free from erythrocytes and casts, but it should be remembered that occasional erythrocytes or granular casts may be found in normal urine. There must have been no history suggestive of nephritis or nephrosis, nor any of the physical signs which are commonly associated with nephritis, such as changes in the vascular system, including retinitis. A slight to moderate degree of anemia, without evidence of renal or vascular disease, was considered permissible. The criteria for a diagnosis of albuminuria with an orthostatic response have differed from those of the first group only in that the albuminuria must have been constantly present in all positions, although increased in grade or amount while the patient was standing. For a diagnosis of chronic latent glomerulonephritis, there must have been a his-

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TABLE I
SUMMARY OF MATERIAL

	Cases	Average age at onset, years	Age of oldest patient	Age of youngest patient	Males, per cent	Patients who were recorded to have lordosis, per cent	Elevated blood pressure, patients	Arteriosclerosis, patients	Elevated blood urea, patients	Reduced excretion of phenol-sulphonphthalein, patients	Fixation of specific gravity, patients	Erythrocytes or casts persistent in sediment, patients	Patients traced	Average number of years traced	Nephritis suspected, patients
Orthostatic albuminuria	100	17.24	47	4	62.0	21.0	1	2					64	6.11	1
Albuminuria with an orthostatic response	43	17.79	46	4	74.4	44.5			1			1	43	7.56	2
Latent glomerulonephritis	17	13.35	32	6	70.6	41.1	1					1	17	8.06	
Chronic glomerulonephritis	25		50	10	56.0		8	2	3	2	13	13			25

tory of acute nephritis which apparently had subsided, although albuminuria had persisted. Although it might have been impossible, without the history, to distinguish this condition from uncomplicated orthostatic albuminuria, traces of albumin in the night specimen of urine frequently have occurred. The albuminuria of chronic glomerulonephritis needs no definition.

In the tables when blood pressure is given, it is the average reading, if more than one observation was made, and is expressed in millimeters of mercury. Hemoglobin was estimated in per cent (Dare). Blood urea was expressed in milligrams of urea in each 100 c.c. of blood, as determined by the aeration method. Excretion of phenol-sulphonphthalein was determined according to the modified method of Rowntree and Geraghty. Albumin was

determined by the sulphasalicylic acid method, and was graded from 1 to 4. Specific gravity was obtained by use of the mercury urinometer of Exton.

ORTHOSTATIC ALBUMINURIA

We studied 100 cases of orthostatic albuminuria. Of these patients 62 per cent were males. However, it is unfair to compare the incidence by sexes, since we do not know the reasons that originally brought the patients to the clinic. Many came because of the discovery of albuminuria in the course of examination for life insurance, and it is probably safe to assume that more males than females apply for life insurance. The average age when the patients were first seen in the clinic was eighteen and twenty-seven hundredths years, while the average age at the time when albuminuria had been

discovered was seventeen and twenty-four hundredths years. The oldest patient was aged 47 years, and the youngest, four years. Twenty-six per cent of the patients were aged 12 years or less, while 7 per cent were aged 30 years or more. The survey disclosed, also, that orthostatic albuminuria is occasionally seen in late middle life, a fact which needs emphasis. Lordosis was recorded as being present in 21 cases and absent in 11; in the remaining 78 cases nothing concerning it was recorded, but it is probably fair to assume that lordosis was absent in most cases.

Forty-nine patients were either observed repeatedly or were known to have had albuminuria previously, and in these cases the average duration of known albuminuria was six and fifteen hundredths years. Seven of the 49 patients responded to a questionnaire, and indicated that they enjoyed good health and had no symptoms of renal disease over an additional average period of five and eighty-nine hundredths years; results of urinalysis were not reported in their answers. Fifteen patients were observed once only; and they answered the questionnaire, an average of six and one-tenth years later, indicating that they were in good health, but they did not report the results of urinalysis. Thus, 64 patients were traced over an average period of six and eleven hundredths years. The remaining 36 patients were observed once only. One patient with persistent orthostatic albuminuria, one of the 64, was observed over a period of 26 years.

Of the 64 patients traced, 63 (98.4 per cent) were in good health after an average interval of six and eleven hundredths years. One of the 64 pa-

tients (1.6 per cent) had symptoms of renal disease, but urinalysis was not reported in this case. Of the 49 patients who were repeatedly observed, 16 (32.7 per cent) had negative urinalysis after an average interval of six and fifteen hundredths years. Thirty-three of the 49 patients (67.3 per cent) still had albuminuria after an average interval of six and fifteen hundredths years. In 11 cases of the 64, casts or erythrocytes were transiently found in the sediment. In four cases, the value for urea was from 40 to 45 mg. in each 100 c.c. of blood, and in three of these cases excretion of phenolsulphonphthalein was normal.

Ophthalmoscopic examination gave evidence of arteriosclerosis in only two cases of the 100. One of these cases was associated with essential hypertension (blood pressure 170 systolic and 130 diastolic), but in this case, six and a half years before, there had been recorded a normal blood pressure and albuminuria of indeterminate type, although tests for orthostatic albuminuria had not been carried out. Albuminuria and occasional casts persisted for three and a half years after the second observation, although there were no symptoms of renal disease. Retinitis was never noted in any case in this group. Only one other patient, and this one was aged ten years, had any evidence of hypertension; blood pressures of 145 and 90 were recorded. This determination was noted as "totally unreliable" however. Ten per cent of the 100 patients had low blood pressure.

ALBUMINURIA WITH AN ORTHOSTATIC RESPONSE

In a second group we studied 43 cases, in all of which the diagnosis of

orthostatic albuminuria was entertained. Patients of this group were observed during the same interval as that during which the first group was observed. It is not permissible to make too strict a comparison between this group and the first group, since only those patients who were traced over a period of years are included here.

Males constituted 74.4 per cent of this group. The average age at which the patients were first seen was nineteen and nineteen hundredths years, and the average age at which the albuminuria was discovered was seventeen and seventy-nine hundredths years. These figures are similar to those noted in the first group. The youngest patient was aged four years; the oldest, 46 years. Thirty-nine per cent of these patients were aged 12 years or less, and 14.3 per cent were aged 30 years or more. There was much less notable segregation of cases between the ages of 13 and 29 in this group than in the previous one. Lordosis was present in 44.5 per cent of the cases, absent in 9.3 per cent, and not specified in 46.2 per cent. Thus, among patients of the second series, lordosis was twice as prevalent as among patients with orthostatic albuminuria.

Forty-two of these patients either were observed repeatedly or were known previously to have had albuminuria. The average duration of observation in this group was seven and seven-tenths years. Two patients were in good health an average of six years after observation, but no report of urinalysis was obtained. One patient was observed only once, and responded to the questionnaire four and one-half years later with the information that there was no difficulty but he gave no

report of urinalysis. Thus, 43 patients were traced over an average period of seven and fifty-six hundredths years. Of these patients, 95.4 per cent were in good health, so far as renal or associated diseases are concerned, after an average interval of seven and fifty-six hundredths years; 4.6 per cent (two patients) had symptoms or urinary findings suggestive of renal disease, after the same interval of years, 39.1 per cent of 42 patients had negative urinalysis after an average interval of seven and seven-tenths years.

This group of patients was similar in many ways, to the series of Maclean,¹ of Lee,² and of Diehl and McKinlay.³ However, certain differences may be noted: (1) the patients were all sufficiently concerned about their general health to consult a physician on their own initiative; the patients in the group observed by each of these other writers underwent a required examination; (2) in our series, the albuminuria was usually persistent, in contrast to the observations of Lee and of Diehl and McKinlay; (3) many of Lee's cases were definite examples of orthostatic albuminuria, and cases of orthostatic albuminuria undoubtedly were present in each of the other series; (4) all of the patients in the cases included by the cited writers were males, whereas our series constituted a mixed group; (5) physical exertion as a factor in producing albuminuria did not obtain in the present series, since many of the patients were at rest in bed in the hospital, and (6) it is well to state that no cases of albuminuria following administration of drugs, serums, or albumin were included in our study.

LATENT GLOMERULONEPHRITIS

Table 2 contains data concerning a group of 17 patients who were known to have had acute nephritis, either in the past or while under observation. The ages ranged from six to 32 years, and only three of the patients were aged more than 21 years. After an interval of eight and six hundredths years, which was the average duration of the time of observation over which results of urinalysis were obtainable, half of the patients were found to have no albumin in the urine, and all were in good health. Lordosis was noted in 41.1 per cent.

Seven of these 17 patients had had scarlet fever, some of whom gave histories suggestive of postscarlatinal nephritis. The remainder gave histories which suggested that they had had acute nephritis, which was either latent when they were first seen at the clinic, as evidenced by the absence of erythrocytes in the urine, or which became latent during the period of observation. Their blood pressures, ophthalmoscopic findings, values for hemoglobin and blood urea and excretion of phenolsulphonphthalein were all within the limits of normal variation.

The principal object in presenting this group is that, aside from the history, 10 of these 17 cases, on a single observation, were in every detail classical examples of orthostatic albuminuria. Such are case 1; case 3, second visit; case 4, second visit; case 5; case 7, second visit; and cases 8, 9; case 10, third visit; 14, and 16. It is of significance that in all of the 17 cases there was an orthostatic response in the albuminuria, and further, that the renal function, so far as it was deter-

mined, was normal in all instances except for the specific gravity determined during the concentration test in two cases. Erythrocytes were observed in the sediment in six cases, in two of which there was acute nephritis at the time. In all but one of these 17 cases there were negative sediments subsequently and there was a question of essential hematuria in this case. Consequently, we feel justified in saying that in this group there was latent nephritis, and in assuming that many of the patients, by the present time, have completely recovered. Furthermore, in these cases which presumably followed acute nephritis there was a period during which, in the process of recovery, an orthostatic response in the albuminuria was a favorable prognostic omen.

Study of the foregoing group shows that often, during the course of latent glomerulonephritis there was an orthostatic element in the albuminuria. Further, during the process of healing, latent glomerulonephritis may exhibit all the characteristics of true orthostatic albuminuria.

CHRONIC GLOMERULONEPHRITIS

A study was made of 25 patients with chronic glomerulonephritis (table 3). Here we were concerned with the relationship of excretion of albumin to the degree of renal insufficiency as evidenced by tests of renal function. Usually, in cases of glomerulonephritis, the blood pressure becomes elevated sooner or later, during the course of the disease; in cases 2, 3, 9, 10, 11, and 22 (table 3) blood pressures were elevated. Ophthalmoscopic examination disclosed retinal changes in cases 10 and 22. Anemia was present in cases 2, 6, 8, 14, and 18. The value for

TABLE II
LATENT GLOMERULONEPHRITIS

LATENT GLOMERULONEPHRITIS																		
Case	Years between onset and beginning of study	Etiology	Age, years and sex	Height, inches	Weight, pounds	Lordosis	Blood pressure, mm. of mercury*		Blood		Excretion of phenolsulphon-phthalein, per cent	Urine				Sediment	Comment	
							Systolic	Diastolic	Hemoglobin, per cent	Urea, mg. for each 100 c.c.		Albumin		Specific gravity	Dilution test			
												Routine	Horizontal					Upright
1	6	Scarlet fever	12F 64 108 21	64 108 21	114	Yes	130 75	78	45	1	0	0	1.001	Negative	Orthostatic albuminuria	Good health		
2	2	Fever?	12F 65 91 21	65 91 21	125	Yes	140 80	75		2	1	2	1.029	Occasional erythrocytes	Negative	Good health		
3	5	Nephritis, edema	15M 65 120 16	65 120 16	132 142	Yes	122 80	78 65	50	2	trace	3	1.025	Occasional cast	Orthostatic albuminuria	Orthostatic albuminuria		
			16 67 132 24	67 132 24			120 65			2	0	1	1.035	Negative	Orthostatic albuminuria	Good health; five years ago negative urine		
4	2	Scarlet fever	14M 67 131 18	67 131 18	153 165	Yes	110 75	80 77 34	65 55	2	trace	2	1.021	Occasional leukocytes	Orthostatic albuminuria	Dental sepsis		
			23 71 165				120 70	77 34		1	0	2	1.028	Negative	Good health			
5	8	Acute nephritis	22F 62 116 30	62 116 30	110	Yes	105 60	75 26	75	2	0	1	1.022	Occasional casts	Septic tonsils, chronic glomerulonephritis	Good health		
6	1	Acute nephritis	15M 66 125 22	66 125 22	150	Yes	115 70	80 26	45	1	trace	2	1.028	Few leukocytes	Focal nephritis	Good health		
7	0.5	Acute nephritis	14M 63 89 15	63 89 15	104 105 70 82	Yes	130 75	72 26	75	2			1.020	Erythrocytes graded 1	Septic tonsils, hypospadias	Hypospadias		
			18				125 70	100 31		2	0	1	1.032	Negative	Hypospadias			
							105 70	82		0				Negative	Hypospadias			
8	1	Scarlet fever	12M 57 81 15	57 81 15	36	Yes	95 60	77 96	61 26	45	2	0	2	1.031	Negative	Phimosi, orthostatic albuminuria	Orthostatic albuminuria	
							No	120 80		2	0	2	1.036	Negative	Orthostatic albuminuria	Nine months before admission hematuria with head cold	Good health	
9	3.5	Scarlet fever	6F 46 10 55	46 10 55	54					2	0	2	1.029	Negative				
										+			1.008					

10	2	Influenza	31M 70 156	135 75	100	24	75	1	0	1	1.024	1.001	Erythrocytes and casts	Focal glomerulonephritis, chronic urethritis, prostatitis graded 1
			33	172	125 85	80 13	85	0		trace	1.030	1.001	Negative	Chronic prostatitis, neuro-muscular pains, anxiety neurosis, mild residual arteriosclerosis
			36	70-174	No	130 85	100 24	75	1	0	1	1.024	Negative	Orthostatic albuminuria, chronic nervous exhaustion; sulfates 2.7 mg. for each 100 c.c. of blood serum
11	0.5	Scarlet fever	16M 66 121 23 69 146	Yes	120 70	83 27	50	3	trace	1	1.030	1.001	Negative	Orthostatic albuminuria Good health
12	10	Scarlet fever	32M 70 179 37 70 174		130 80	80 26	50	1	trace	1	1.031	1.001	Negative	Orthostatic albuminuria Good health
13	1	Tonsillitis?	21M 70 150		140-75	75 17	85	4	2	1	1.021	1.001	Granular casts, erythrocytes, graded 2-3	Focal nephritis?
			21	70 150	125 75	76 25	75	2	1	1	1.025	1.001	Erythrocytes, graded 2	
			23	147	140 95	82 14	60	1	trace	2	1.036	1.001	Negative	Latent glomerulonephritis
			27	70 153				0					Negative	Good health
14	7		15M 70 140		100 60	100 20	45	1	0	1	1.029	1.003	Occasional leukocytes	Acute nephritis 3 weeks ago; albuminuria 7 years
			17			31+	50	1	trace	1	1.032	1.003		
15	0	Acute nephritis	15M			70		1			1.024	1.002	Erythrocytes graded 2, occasional cast	Acute nephritis
			19	154	125 70	76 24	85	1	trace	1	1.025	1.001	Erythrocytes, graded 3	Essential hematuria?
			22	69 162	No			0			1.014		Occasional erythrocytes	
16	3	Scarlatina	9F 55 62 16 68 109	Yes		73		1	0	1	1.009	1.001	Negative	Orthostatic albuminuria Good health
17	0	Subacute nephritis	18M 133 25 71 156		110 65	78 38	60	2			1.020	1.001	Erythrocytes, graded 2	Subacute glomerulonephritis
					110 75	71 32	80	2	trace	1	1.030	1.002	Negative	Colloid goiter, albuminuria

*Ocular fundi were negative in all cases.

†In some cases this represents a reading obtained at routine examination of the urine; in other cases, a reading obtained on concentration test.

‡Non-protein-nitrogen.

TABLE III
CHRONIC GLOMERULONEPHRITIS

Case	Age, years and sex	Height, inches	Weight, pounds	Blood pressure mm. of mercury*		Blood		Excretion of phenolsulphon-phthalein, per cent	Albumin			Specific gravity		Sediment	Comment	
				Systolic	Diastolic	Hemoglobin, per cent	Urea, mg. for each 100 c.c.		Routine	Horizontal		Upright	Concentration test			Dilution test
1	23F	69	130	125	85	75	30	45	2	2	3	1.020	1.001	Erythrocytes, casts	Chronic glomerulonephritis	
2	21F	64	121	140	100	62	30	75	2	1	3	1.028	1.005	Negative	Chronic glomerulonephritis, insidious	
3	25F	69	158	165	120	72	13	80	1	2	3	1.025	1.003	Erythrocytes, casts	Chronic glomerulonephritis	
4	50M	68	155	120	70	83	25	75	trace	1	2	1.029	1.002	Negative	Chronic glomerulonephritis, latent	
5	16M	61	135	135	85	76	24	30	3	2	3	1.025	1.002	Erythrocytes, casts	Chronic glomerulonephritis	
6	17F	67	146	115	80	68	16	60	2	1	2	1.030	1.002	Negative	Chronic glomerulonephritis, insidious	
7	17M	70	130	130	60	77	24	55	2	2	2	1.021	1.004	Negative	Chronic glomerulonephritis, latent	
8	33F	63	110	120	70	62	20	75	4	4	3	1.020	1.001	Occasional erythrocytes	Chronic glomerulonephritis, insidious, mitral stenosis	
9	16F	66	111	140	90	72	16	75	2	trace	trace	1.030	1.001	Negative	Chronic glomerulonephritis, insidious	
10	46M	65	140	145	95	98	29	75	4	1	1	1.035	1.001	Casts, occasional erythrocytes	Chronic glomerulonephritis, insidious	
11	41M	68	164	145	90	90	36	80	2	trace	trace	1.029	1.001	Negative	Chronic glomerulonephritis, insidious	
12	31M	69	153	145	85	73	30	60	4	3	3	1.030	1.002	Erythrocytes, casts	Chronic glomerulonephritis, insidious	
13	23M	71	157	130	85	91	20	70	2	2	2	1.010	1.009	Negative	Chronic glomerulonephritis, latent	
14	14M	64	101	160	100	61	54	45	4	4	4	1.016	1.004	Erythrocytes	Chronic glomerulonephritis	
15	38M	71	143	130	95	80	22	70	2	1	1	1.026	1.001	Granular casts	Chronic glomerulonephritis	
16	31F	62	117	130	80	75	22	80	2	1	1	1.025	1.001	Negative	Chronic glomerulonephritis	
17	19M	73	154	110	65	80	28	70	2	2	2	1.032	1.001	Negative	Chronic glomerulonephritis, latent	

18	16M	67	145	140	70	75	34	75	2	trace	2	1.030	1.003	Occasional cast, erythrocytes graded 1 to 2 Negative Erythrocytes graded 2, casts	Focal nephritis ?
17			120	80		90	67	2						Chronic glomerulonephritis ; patient died 3 years later in uremia ; no necropsy	
19	67	135	140	90	68	37	40	4	3	1.016	1.003				
19	31M	69	135	140	95	73	38	65	2	trace	1	1.021	1.001	Erythrocytes, casts	Orthostatic albuminuria, benign hypertension Chronic glomerulonephritis, verified at necropsy
20	39M	73	139	145	90	82	30	60	1	0	trace	1.023	1.002	Hyaline casts, graded 3, erythrocytes graded 2	Chronic prostatitis, focal nephritis ?
21	15F	64	110	110	75	78	30	45	3	0	3	1.013		Negative	Residue of chronic glomerulonephritis
	16	64	112	140	90	72	72	35	2	2	3	1.016	1.003	Negative	Chronic glomerulonephritis
	17	63	108	120	80	70	40	35	1			1.015	1.003	Negative	
	17		120	140	90	71	41	15	3	3	3	1.014	1.003	Negative	
	17		108	135	100	70	80	15	2			1.010	1.001	Negative	
	18		130	80		91	10	2			+	1.008			
	19														Chronic glomerulonephritis ; verified at necropsy
22	30F	62	156	210	120	77	22	60	4	0	1	1.023	1.001	Casts and erythrocytes	Benign hypertension, chronic nephrosis, orthostatic albuminuria
23	13F	60	74	110	80	100	18		2	1	2	1.026		Occasional erythrocytes	Enuresis
24	22M	69	123	130	85	94	32	80	4	1	3	1.036	1.001	Hyaline casts, erythrocytes graded 1	
	24	69	139	110	78				1			1.024	1.001	Negative	Good health
25	10F	54	64	95	75	80			2	0	2	1.030		Leukocytes, graded 1, erythrocytes graded 1	Faulty posture, albuminuria, neuropathy

*Retinal changes present in cases 10 and 22 only.

blood urea was elevated in cases 14, 18, and 21, whereas elimination of phenol-sulphonphthalein was diminished below the lower limits of normal in cases 5, 18, and 21. In all cases except 20, 21, 22, and 25, albuminuria persisted while the patient was reclining. Impaired concentrating or diluting power of the kidneys was seen in cases 1, 3, 5, 7, 8, 13, 14, 16, 18, 19, 20, 21, 22, and 24. Erythrocytes were noted in the sediment in cases 1, 3, 5, 8, 10, 12, and 14, and in cases 18, 19, 20, 22, 23, 24, and 25 inclusive.

It is important to note that, in all these cases, the glomerulonephritis was sufficiently mild (at least on first observation) to warrant considering the possibility of orthostatic albuminuria. Case 21 fulfilled all the requirements of orthostatic albuminuria on first observation, although fifteen months later renal function had become markedly impaired. This is the only instance of this sequence.

It is apparently possible to make a correlation between the impairment of renal function, as shown by the usual tests of function, and the response of the kidneys to the orthostatic test. Thus, in 19 of the 25 observations (76 per cent) a direct relationship between diminution of excretion of albumin in the horizontal position, as compared with that in the erect position, and the degree of renal impairment as measured by dilution and concentration tests, may be noted. If there was diminution in the amount of albumin excreted, renal function was adequate as measured by the other tests; and, conversely, when albumin did not diminish, renal function was impaired as measured by the other tests. In eight cases there was no diminution in albu-

min in the presence of impaired renal function, and in 11 cases there was diminution of albumin in the presence of good function, a total of 19 cases. In one case there was no diminution of albumin, but good function; and in five cases there was diminution with poor renal function. In grouping these cases allowance was made for the effect on specific gravity of large amounts of albumin.

FOCAL INFECTION AND WEIGHT IN ALBUMINURIA

Calvin, Isaacs, and Meyer⁴ commented on the high incidence of focal infection among patients with orthostatic albuminuria. In our study, foci of infection occurred with practically the same incidence in association with orthostatic albuminuria, and in association with albuminuria with an orthostatic response. Removal of foci did not appreciably influence the albuminuria in either group. By "foci of infection" we refer to obviously diseased tonsils, teeth, sinuses, or prostate gland, or to a chronic suppurative process, such as bronchiectasis or otitis media. Border-line cases were not included.

Practically all observers have recorded the typical asthenic habitus of patients with orthostatic albuminuria, and the implication is often noted that, with gain in weight after adolescence, albuminuria tends to disappear. In order to gain some accurate information on this point, the recorded weight in each case of orthostatic albuminuria has been compared with the standard normal weight of persons of the same age, sex and height, as given in the tables based on medical actuarial statistics. This has been recorded in percentage of variation above and below

the average normal. Figure 1 shows the averages in the cases of orthostatic albuminuria, and figure 2 the averages in the cases with other forms of albuminuria. It will be seen that there is no striking difference between these groups, both falling chiefly in the normal to minus 10 per cent zone. With

been strengthened by the observations of Russell⁶ and of Weiss-Eder.⁷ Fishberg⁸ inclined somewhat to this view. We are able to add a series of seventeen cases in which true orthostatic albuminuria, or albuminuria with an orthostatic response, dated presumably from acute nephritis. We assume that

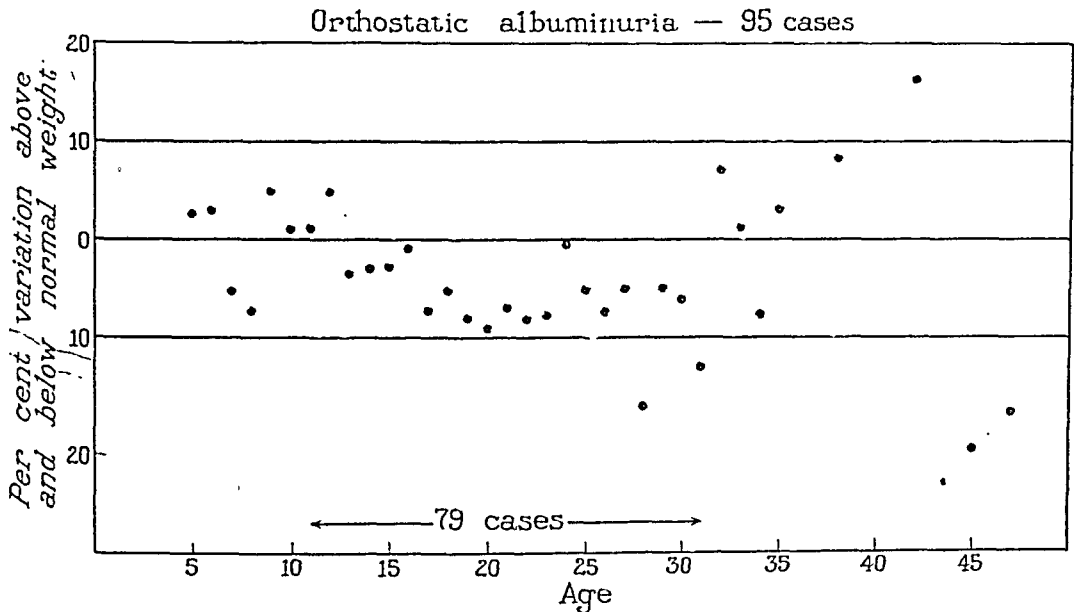


FIG. 1. Average percentage variation, above and below normal, of weight of 95 patients with orthostatic albuminuria. Each spot represents the patients of one age-group. Seventy-nine of the 95 patients were between the ages designated by the positions of the arrow heads, and the weights of most of these 79 patients were within the normal to minus 10 per cent zone.

the passage of years, there is no constant relationship between change in weight and persistence of the albuminuria in cases of orthostatic albuminuria.

COMMENT

Among the conflicting reports, the only hypothesis concerning etiology, which has not been refuted, is that of Senator,⁵ who reiterated many times in the course of several years, that albuminuria detectable by ordinary clinical tests is never "functional". This hypothesis concerning renal injury has

orthostatic albuminuria or albuminuria with an orthostatic response means persistent renal injury which frequently heals completely. We believe that the burden of proof rests with those who ascribe orthostatic albuminuria to causes other than renal injury. In one case in the first group, the injury presumably went on to nephritis, and cases 20, 21, and 22, in table 3, were definitely cases of chronic glomerulonephritis, although albumin was absent from the night urine.

It is possible to avoid error, to a great extent, by insisting on the fol-

lowing points before making the diagnosis of orthostatic albuminuria: (1) absence of even traces of albumin in the urine excreted with the patient recumbent; (2) absence of persistent erythrocytes or casts, or more than an occasional erythrocyte or cast in the sediment; (3) absence of a history or of physical signs of nephritis or ne-

more so than the other patients studied, and changes in weight have no effect on the incidence of albuminuria. It should be noted that the albuminuria may persist through middle life.

Among patients who have albuminuria with an orthostatic response, the prognosis is almost as good, but the diagnosis must be established with the

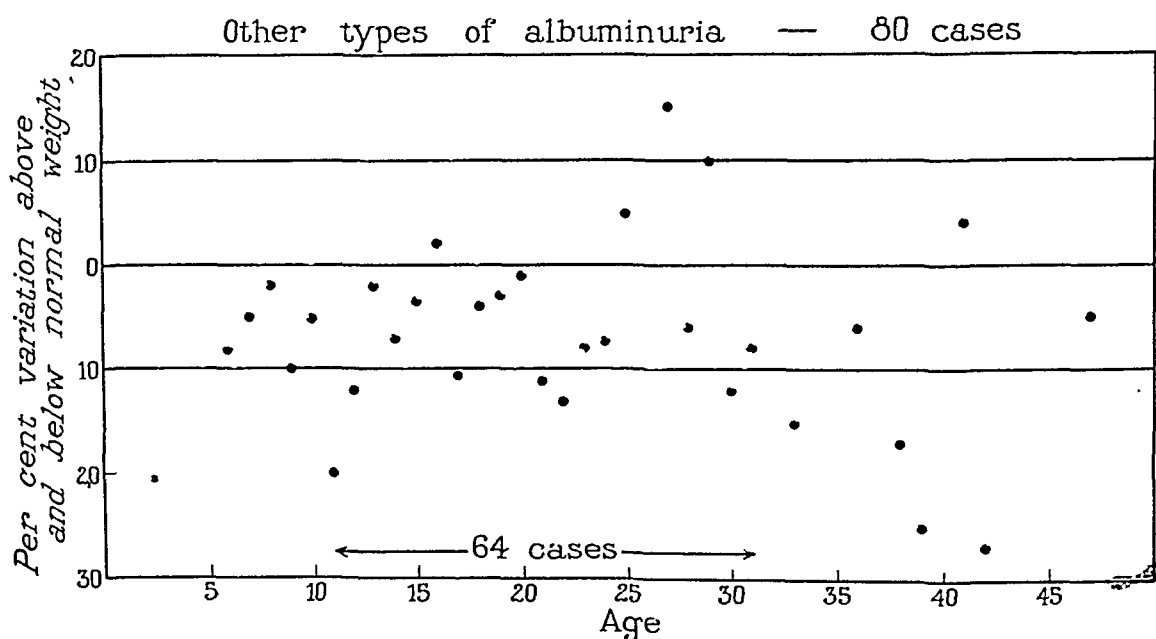


FIG. 2. Average percentage variation, above and below normal, of weight of 80 patients with albuminuria of other than orthostatic type. Each spot represents the patients of one age-group. Sixty-four of the 80 patients were between the ages designated by the positions of the arrow heads, and the weights of most of these 64 patients were within the normal to minus 10 per cent zone.

phrosis or associated vascular changes; (4) normal renal function, as measured by the usual tests, and (5) observation of the patient over a period of several months. A correct diagnosis of orthostatic albuminuria carries with it a prognosis of good health and longevity in 99 per cent of cases, and a probability that, in 33 per cent, the urine will become free of albumin. There is no evidence that foci of infection play any part in the causation of orthostatic albuminuria. The patients are slightly underweight, but no

same care as in orthostatic albuminuria. We believe that albuminuria with an orthostatic response indicates a more marked degree of renal injury.

When a diagnosis of latent glomerulonephritis is considered, a period of several months of observation is necessary, to be sure that one is not dealing with slowly progressive chronic glomerulonephritis. Although the outcome in our small group of cases of latent glomerulonephritis was as good, or was better, than that in the groups of cases of orthostatic albuminuria, or of cases

of albuminuria with an orthostatic response, we feel that, in general, the prognosis should be more guarded. The presence of an orthostatic element in all of our cases may well have a relationship to their unusually good outcome. The development of orthostatic albuminuria in the course of acute nephritis seems to indicate partial recovery, and may be of aid in establishing a prognosis.

Although the existence of an orthostatic element in chronic glomerulonephritis has been frequently observed, we are not able to find record of any attempt to correlate it with tests of renal function.

The etiology of orthostatic albuminuria is not known. However, a few facts about man's excretion of urine due to his upright position, may help to explain orthostatic albuminuria. For instance, excretion of water by normal kidneys has been shown to be decreased by the upright position.⁹ There is some evidence in favor of the belief that excretion of such a substance as urea may, also, be so affected. If some sort of mild renal injury is assumed, then the following concepts are applicable: when the patient is recumbent, function is enhanced, water and such substances as urea are excreted more easily, and albumin not at all. As soon as the upright position is assumed, the kidney is not able to readjust itself, and there is loss of albumin. Furthermore, in support of this view, we have shown that in chronic glomerulonephritis, when

renal injury progresses sufficiently to be demonstrable by the usual tests of function, the element of orthostatic albuminuria disappears. Also, in selected cases, during recovery from acute nephritis, a period characterized by orthostatic albuminuria is not uncommon. Therefore, orthostatic albuminuria is probably in the range of mild renal pathologic physiology.

CONCLUSIONS

1. Strict diagnostic criteria must be observed before a patient is considered to have orthostatic albuminuria.

2. The prognosis is excellent in cases of orthostatic albuminuria, although the albuminuria may persist through middle life.

3. The diagnosis of albuminuria with an orthostatic response requires similar careful consideration, and carries almost as good a prognosis.

4. Among patients who have had acute nephritis, the development of an orthostatic element in the albuminuria apparently indicates partial recovery and a good prognosis.

5. In chronic glomerulonephritis there is some evidence that the presence of an orthostatic element in the albuminuria indicates adequate renal reserve, and its disappearance may be a sign of renal insufficiency.

6. From the data presented regarding the etiology of orthostatic albuminuria it would appear that the burden of proof rests with those who do not consider it due to renal injury.

BIBLIOGRAPHY

¹MACLEAN, H.: The incidence of albuminuria and casts in British soldiers during training and the relationship of this con-

dition to war nephritis, *Brit. Med. Jr.*, 1919, i, 94-98.

²LEE, R. L.: Albuminuria in young men,

- Med. Clin. N. Am., 1920, 3.2, 1059-1063.
- ³DIEHL, H. S., and MCKINLAY, C. A.: Albuminuria in college men, Arch. Int. Med., 1932, xlix, 45-55.
- ⁴CALVIN, J. K., ISAACS, B. L., and MEYER, J.: Albuminuria in children, Jr. Am. Med. Assoc., 1926, lxxxvi, 1821-1824.
- ⁵SENATOR, quoted by HOOKER, D. R.: Postural or orthostatic albuminuria; a critical summary of the literature, Arch. Int. Med., 1910, v, 491-509.
- ⁶RUSSELL, J. W.: Origin and significance of postural (orthostatic) albuminuria, Lancet, 1925, ii, 683-688.
- ⁷WEISS-EDER, S., quoted by BASS, M. H.: A summary of the recent literature on orthostatic albuminuria, Am. Jr. Dis. Child., 1912, iv, 246-256.
- ⁸FISHBERG, A. M.: Hypertension and nephritis, Ed. 2, 1931, Lea and Febiger, Philadelphia.
- ⁹WHITE, H. H., ROSEN, I. T., FISCHER, S. S., and WOOD, G. H.: The influence of posture on renal activity, Am. Jr. Physiol., 1926, lxxviii, 185-200.

Addison's Disease and Its Relation to Experimental Adrenal Insufficiency*†

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ALTHOUGH the first accurate description of the adrenal glands is usually accredited to Eustachius, in 1563, very little further progress was made in the study of their structure or physiological significance for nearly three centuries and practically all of the further additions to our knowledge have been made within the past eighty years. Modern interest in the adrenals dates from Addison, who published in 1855 the clinical observations on the disease which bears his name.

In all mammals, including man, the adrenal glands are paired organs, each composed of two distinct parts. The outer layer, or cortex, forms roughly two-thirds to three-quarters of the whole, and this surrounds the inner portion, or medulla, which is of distinct and separate embryological origin. Until very recently the attention of most investigators has centered upon the medulla, which has been shown to be closely related in its origin to that of the nerve cells of the sympathetic ganglia and in its later

development and functional significance to the sympathetic nervous system.

There is both an anatomical and a physiological reason for the greater interest which has been displayed in the adrenal medulla. In 1865 Henle first showed the peculiar affinity of the medullary tissue for the salts of chromic acid, and the characteristic brownish-yellow staining reaction of these chromaffin, or chromaphil cells when treated with this chemical was of prime importance in their identification.

The second reason for the greater interest in the adrenal medulla lies in the fact that extracts of this chromaffin material possess peculiar and characteristic physiological properties, readily observed and measurable with relative ease, although with uncertain accuracy. The substance itself which we now know as adrenalin was finally obtained in crystalline form and subsequently produced synthetically just about thirty years ago. For a number of years the discovery of adrenalin naturally focused attention upon the adrenal medulla to the exclusion of interest in the cortex, since it was demonstrated with reasonable conclusiveness that adrenalin originates solely in the medulla, its presence in the cortex being due to postmortem diffusion. The advances which followed the isolation

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of adrenalin furnish a striking example of the fact that progress in knowledge of any endocrine gland secretion is in direct proportion to the availability of a simple quantitative measure of its physiological effects.

Chromaffin tissue is widespread in its distribution. Stilling, and later Kohn, showed that groups of cells occur throughout the course of the sympathetic nervous system, either as microscopic clusters in the ganglia or as macroscopic bodies in the sympathetic plexuses called "paraganglia". In addition to similarity in morphology and in the chromaffin reaction, extracts obtained from this extra-medullary tissue exhibit similar physiological properties to like preparations derived from the medulla itself. Indeed, according to Biedl, in the new-born, in whom very little adrenal medulla exists, the action of these extra-adrenal extracts, particularly those from the abdominal chromaffin body, are more effective upon constriction of blood vessels than those from the adrenal medulla itself. This abdominal chromaffin body remains of considerable size until the child is one year of age, after which it degenerates. In other forms, as in the dog, cat, and rabbit, it is an organ of significant size throughout life. Kohn showed by accurate determinations of the respective weights that the abdominal chromaffin body in the adult dog may represent as much as one-quarter of the total weight of the medulla itself.

Studies leading to such knowledge as we now possess of the physiological significance of the cortex really antedate those on the medulla, although they were not at the time so recognized. The original description of Addison's disease was the stimulus which

led Brown-Sequard in 1857 to test the effect of removal of the adrenals in a number of different species, including rabbits, dogs, guinea-pigs and cats. A fatal result invariably followed their bilateral removal within thirty-seven hours and this led him to the view that the adrenals are essential to life. There is no doubt that this correct conclusion, in the light of present day knowledge, was based upon experiments in which the animals died, not of adrenal insufficiency, but of surgical shock or of sepsis. It is possible with proper surgical technic, using dogs, even when both glands are removed at one operation, to have survival without any treatment for at least seven days. The effect, however, is ultimately that described by Brown-Sequard. If insufficient accessory adrenal tissue is present, the animal invariably dies.

The question then arose as to whether the part of the gland indispensable for life was the medulla, the cortex or the adrenal tissue as a whole. Through the efforts of a considerable group of observers it has been shown during the past two decades that the cortex of the gland is the vital structure, since destruction of the medulla by extirpation or by a number of other means, such as cauterization or radiation, permits the animal to live on. So long as the cortex, or at least a fraction of it (from one-fourth to one-eighth), is left intact, the animal does not seem to suffer ill effects. It has, therefore, been generally accepted in recent years that the cortex is the essential structure. The medulla and the chromaffin tissues generally have been tacitly relegated to a position of minor importance. This view has undoubtedly been strengthened by the success

substitution therapy with lipid soluble extracts of the cortex in totally adrenalectomized animals, as demonstrated by Hartman, by Swingle and Pfiffner, and by others within the past two or three years.

It is well to bear in mind, however, that the question of the importance to life of the chromaffin tissues as a whole has never been brought to rigorous test. Owing to their widespread distribution they cannot be completely extirpated, as can the cortex in most forms, where accessory cortical tissue in significant amounts does not exist. We must conclude that the indispensability of the medulla yet remains to be disproven, and that it is at the present moment unknown whether the close juxtaposition of these two portions of the adrenal gland differing so widely in origin, morphology, and chemical properties, is pure accident or is of vital and fundamental significance.

Certain facts, however, have been gathered which make it appear that the close approximation of these two tissues in the mammal may not be altogether a coincidence. In some of the lower vertebrates, as in the elasmobranch fishes, the tissues which correspond to the adrenal cortex and medulla are separated, the cortex being represented by the interrenal body and the medulla by the paired bodies which lie close to the ganglia of the sympathetic chain. In birds and reptiles, and in amphibians, the renal and adrenal tissues interlock. It is only in mammals that the same condition is found as in man—the adrenal is composed of a central medulla with an enclosing cortex.

In most mammals, as is well known, the cortex is divided by the morpholo-

gists into three zones. The cells in the central portion are arranged mainly in columns, the zona fasciculata. The portion next to the medulla is a network of trabeculae, the reticularis. At the surface the columns end in rounded terminations, the so-called glomerulosa.

The blood supply of the adrenal gland is of particular interest. Per unit of weight it is more abundant than that of any other body organ, being estimated as 6 to 7 c.c. per minute for each gram of tissue, higher even than the thyroid, which comes next with 5 c.c. per gram per minute. The arteries divide in the cortex into capillary plexuses which fuse into sinuses in the reticularis, the innermost zone of the cortex, and go over by numerous and free communication into the venous sinuses of the medulla. A second supply to the medulla is from branches which perforate the cortex without division. Present evidence indicates that a very considerable proportion of the adrenal blood supply passes first through the cortical layers of the gland and thence into the medulla, so that materials given off into the blood stream in the cortex, in large part, at least, have opportunity to come into contact with the cells of the medullary portion of the gland. The blood from both regions unites to pass out in the same venous channels.

Because of the fact that it has been shown to be an indispensable portion of the gland, attempts to isolate an extract which would prolong the lives of adrenalectomized animals have usually been made with material from the dissected adrenal cortex alone. The medulla, containing the bulk of the adrenalin, was discarded. Improved technical methods, however, have recently

made it possible to get rid of adrenalin and other toxic products with comparative ease, so that the whole glands may be used for the manufacture of the extract, thus avoiding the laborious preliminary separation of medulla and cortex.

Pfiffner and his collaborators at Princeton, using the method of biological assay of the cortical hormone, which was devised last year in our laboratory at Baltimore and which is based upon the minimal per kilo maintenance dose in the adrenalectomized dog, have recently shown that extracts prepared according to the Pfiffner-Swingle method from whole beef adrenal glands have several times the potency of extracts made from dissected beef cortex alone, based on equivalent weights of tissues. This remarkable fact we are able to confirm. Extracts of dissected cortex material alone have an assay value of six to ten dog units per c.c. of material, while extracts prepared from whole beef adrenal glands may have an assay value of forty units per c.c. or even more. The method of assay which we have employed is, we believe, accurate to within 25 per cent of the true value. If well-nourished animals in prime condition are used the results under these conditions are readily reproducible.

This increase in the potency of extract prepared from the whole glands as compared with that from the dissected cortex is somewhat difficult to interpret on the basis of the long held assumption that the cortex as a whole is the site of origin of the hormone essential to life. This difficulty is increased by a recent paper by Cleghorn,¹ who found that extracts of the (skate)

elasmobranch interrenal body, which as we have stated above is distinct in this form from the segmentally arranged chromaffin bodies, and may be dissected quite separately from them, is without effect in reviving or maintaining the adrenalectomized cat.

In an attempt to throw further light on these puzzling and conflicting findings, my associates, Dr. J. H. Trescher, and Dr. L. J. Soffer, and I have undertaken comparative assays of extract made from: (1) cortical tissue prepared free of medulla by taking thin slices from the periphery of the gland cleaned and dissected away from the surrounding tissues and fat; (2) cortical tissue prepared in the usual manner by splitting the gland longitudinally and dissecting out the medulla; (3) the medulla tissue dissected quite free of cortex; and finally (4) the whole gland material. The material for this study was obtained on the slaughtering floor of one of our large abattoirs immediately after removal from the beef carcass. As rapidly as it was dissected out it was thrust into 95 per cent alcohol to prevent destructive enzyme activity, and frozen solid with carbon dioxide snow. The following assay values on glands so prepared and derived from the same source have been obtained for equivalent weights of tissue:

PREPARATION OF EXTRACT

1. Cortical tissue from the periphery, not in contact with medulla, less than 3 dog units per c.c.
2. Cortical tissue prepared in the usual manner, 8 dog units per c.c.
3. Medullary tissue, 8-10 dog units per c.c.
4. Whole gland tissue, 15-20 dog units per c.c.

These results indicate the higher

concentration of the potent principle as we approach the medulla and the relatively low concentration in the outer part of the cortex of the beef adrenal. Complete separation of cortex and medulla is very difficult. Portions of medullary tissue must be present in the dissected cortex prepared according to the original technic, while the dissected medullary tissue undoubtedly contains fragments of cortex, especially of the reticular layer.

In the light of our fragmentary knowledge both of the chemical properties and of the function of the new hormone, it is most plausible to account for its greater concentration near or in the medulla on the supposition either that it is stored in the larger venous sinuses, or that it is bound to some protein or other structure present in the medulla, so that diffusion from cortex into medulla may continue and increase its concentration in the latter portion of the gland.

It may be interesting, however, to draw your attention to another possibility to account for this curious and unexpected distribution of the hormone within the gland. This is that the site of final activation of the so-called cortical hormone (or "cortin") actually lies in the outer portion of the medulla itself, or in the reticular layer of the cortex which immediately adjoins it. The findings are compatible with the assumption that the cortex elaborates a precursor which is converted into the active substance in this region of the gland. The blood supply of the adrenal gland, in which blood from medulla and cortex are joined together in this border area would favor such a possibility.

The mechanism above outlined would explain not only the indispensability to life of the interrenal body of the elasmobranch, as shown by Biedl, but, on the other hand, the seemingly contradictory finding that extracts of this organ, according to Cleghorn, do not contain the "life" hormone. It will also explain the variations in amount of active material in the several parts of the gland as found above. The survival of animals in which the medulla of the gland has been destroyed or removed, leaving the cortex intact (assuming that such complete elimination is really possible) may be explained by the presence of accessory medullary tissue which, as I have just stated, occurs in large amounts. The presence of smaller amounts of the hormone in the outer layers of the dissected cortex could then be explained in the same manner as the occurrence of adrenalin in the cortex, namely, as due to diffusion into the outer cortical portion of the gland post mortem. The enhanced potency of material derived from the whole adrenal glands prepared in the usual way may well be due to the intimate admixture of the chopped-up tissue during the course of preparation of the extract, or to lessened exposure to the air.

The main cause of Addison's disease is bilateral tuberculosis of the adrenal glands. It was formerly believed that the adrenal infection is primary, but it is now realized that this lesion is usually associated with latent or active tuberculosis elsewhere in the body, probably in most instances in the lungs. Tuberculosis of the adrenals is a relatively rare disease having, it is said, about the same incidence as tubercu-

losis of the skin. The tuberculous lesion appears to attack the medulla first and later the cortex. The latter always seems to be affected, however, in reliable reports of Addison's disease. Wiesel found in a fifteen-year-old tuberculous patient with complete destruction of the medulla, but intact cortex, no symptoms of the disease, although the paraganglia, significantly enough, were much enlarged.

In approximately one-fifth of the published cases but in a larger proportion of our present series, the lesion found at autopsy in the adrenal glands is that of primary cortical atrophy. A very considerable number of such cases has now been reported, and it is of interest to note that in them, in contrast to the cases of tuberculosis of the adrenals, it is the cortex which is first and principally affected while the medulla is seriously altered only at a later period. Our fatal cases of Addison's disease associated with this primary cortical atrophy have been studied by Duff and Bernstein²; we have had four come to autopsy. The destructive process was a progressive necrosis of cortical cells with collapse of the stroma. The reticular zone disappeared first and of the two other zones the outer one, the glomerulosa, persisted longer. Regeneration appeared as islands of newly formed cells at the periphery. More or less dense infiltrations of lymphocytes were always present in the medulla and among the remains of cortical tissue. The necrosis of the cortical cells was accompanied by relatively little fibrosis, the outer capsule simply collapsing down to the medullary tissue.

Duff was able to find four less ad-

vanced cases of adrenal atrophy in which a similar destruction had taken place, with small lymphocytic accumulation and without changes in the medulla. In these cases without symptoms of Addison's disease, the primary lesion was in the cortex, and the reticular zone was most susceptible, the glomerular most resistant, to destruction.

It seems to us of importance from the point of view of therapy that areas of regeneration occur in the injured glands. The quick response of the remaining cortical tissue to the stimulus of deficiency is striking. In the experimental animal, after removal of one gland, hypertrophy of the remaining adrenal gland is very rapid, and quite definite in the dog within three or four weeks. This hypertrophy is decidedly greater in the presence of infection, distemper in the dog being an especially effective stimulus. It is not unusual in such cases to find the second gland double the weight of the one first removed. This increase is confined so far as we can determine to the cortical portion. When sufficient extract is supplied to the adult male dog from which one gland is removed this hypertrophy is not found, indicating that lack of this material is the adequate stimulus for production of the hypertrophic change. Injections of the extract will not, however, prevent hypertrophy of the remaining gland in a growing animal, or in the presence of malnutrition, or of an intercurrent infection, even in doses per kilo of body weight which are otherwise effective in the healthy adult. We believe this to be suggestive evidence that products of the cortical tissue are required in greater amounts by the growing animal,

as well as by the animal during the course of an infection, and that further studies along this line may be of help in reaching a better understanding of this phase of cortical function.

One of the cardinal features of Addison's disease is pigmentation. In many it is the first symptom observed and often one finds that the earliest change the patient notes is that of a summer's tan which does not fade. It may be present for many years and it has been repeatedly observed that such cases are apt to be more prolonged and to run a more benign course than those ushered in by asthenia and muscular weakness. A recent case observed by us is of interest:

G. F., a white man of 55, works for a life insurance company which gives periodic health examinations to its employees. Owing to this it is known that he has had low blood pressure since 1917. During 1917 and 1918 he was in a sanitarium for sixteen months with pulmonary tuberculosis. One daughter has died of pulmonary tuberculosis, but the contact with the patient was not close. He has felt quite well. There have been no gastrointestinal symptoms and no muscular weakness prior to his present illness. He came to the hospital this autumn with influenza complicated by pneumonia and there it was noted that he had marked and characteristic pigmentation of lips and buccal mucosa, which he stated on questioning had been present for many months. During recovery from his influenzal infection the asthenia has improved and at the present time he is free of symptoms. He has never received cortical extract.

We have here a patient whose history and appearance is highly suggestive of Addison's disease, with proven hypotension for many years and with pigmentary changes for many months. It seems quite possible that in this instance we are dealing with tuberculosis of the adrenals and that the process

has so far attacked chiefly the medulla while the cortical portion is as yet largely unimpaired.

Speculation as to the relationship of the pigmentation to the disease has naturally centered about the close similarity of chemical structure between adrenalin and the skin pigment, melanin. It has been suggested that failure of the gland to utilize the natural adrenalin precursors to form adrenalin has led to their vicarious utilization in the skin in the formation of increased amounts of melanin. The supposed precursor most popular in the minds of investigators is dioxyphenylalanin or "dopa", which has been studied by Bloch and his pupils. Unfortunately, it has not been possible to produce such skin pigmentation experimentally by removal of the adrenal glands in animals and the positive results reported from time to time cannot be regularly reproduced. Scars, pressure, exposure to various chemical and physical agents, including light, produce no pigmentation not also to be observed in control animals. The injection of dioxyphenylalanin itself in rats and in dogs without adrenal glands is without effect. Patients with Addison's disease during the relapse often show marked increase in pigmentation, and improvement is frequently but not regularly associated with its partial disappearance. With the aid of Professor Max Brödel and his pupils we have been measuring the depth of pigmentation in our patients over definite skin areas during the various phases of the disease. We find that when these changes are measured by such objective criteria our clinical impressions have often proved very faulty. Increases appear rather quickly especially during re-

lapses but disappear very slowly, probably by wearing away of the basal cell layer in which the pigment is deposited in the natural course of skin growth. Differences measured over the course of months are indeed quite definite, but no marked disappearance of the pigmentation has occurred even after much extract has been given.

Now as to the results of treatment of patients with the new cortical extract. We have treated during the past two and one-half years thirteen patients whom we regard as definitely suffering from Addison's disease. Of these, seven have died. The diagnosis in all of them was confirmed by autopsy. (Table 1) C. L., the first case

assay, probably due to imperfect preservation of the glands at the abattoir during the hot weather. F. R. died at a sanatorium of disseminated tuberculosis throughout the body. His condition was hopeless from the outset and the wisdom of treating such cases, when limited supplies of the extract are available, is of course open to grave doubt. The other four fatal cases were those due to cortical atrophy and the lesions found have already been discussed.

It is quite evident that the hopes aroused three years ago as to the value of the cortical extract or cortin in the treatment of Addison's disease have not met with as complete satisfaction

TABLE I
CASES OF ADDISON'S DISEASE TREATED WITH ADRENAL CORTICAL HORMONE
WITH FATAL OUTCOME

Patient	Age	Sex	Duration of illness before treatment	Duration of treatment	Number of relapses	Weight gain after treatment	Outcome Autopsy Diagnosis
C.L.	50	F	6½ yrs.	8 wks.	4	No increase	Tuberculosis of adrenals
E.S.B.	34	M	22 mos.	8 mos.	3	No increase	Cortical atrophy with symptoms of asthma
R.M.C.	36	F	8 yrs.	9 mos.	6	No increase	Cortical atrophy; cirrhosis of liver with jaundice
M.S.	37	F	4½ yrs.	15 mos.	4	No increase	Cortical atrophy; acute fibrinous pericarditis
M.D.	35	F	6 mos.	10 mos.	2	No increase	Cortical atrophy.
G.K.	48	F	4 yrs.	23 days	1	No increase	Tuberculosis of adrenals and cold abscess of rib
F.R.	42	M	11 mos.	80 days	3	No increase	Tuberculosis of adrenals, lungs, kidneys and liver

treated in the fall of 1930, did not receive adequate amounts of extract according to our present standards. G. K. was treated for twenty-three days last summer with an extract of low potency, as was later found on

as was originally anticipated. There can be no doubt, we believe, of the value of the material in the acute relapse of the disease. It should be given in large amounts at as early a time as possible. We have never seen evidence

of overdosage in the experimental animal. We have administered 100 c.c. intravenously to an 8 kg. dog without the slightest evidence of toxicity and we have never noticed any harmful effect clinically from the use of any of the extracts prepared in our own laboratory. It appears possible that the extract alone in certain cases without the aid of any accessory agent can relieve the acute crisis, as is indicated by

circulatory collapse. Insofar as the cortical hormone appears to restore the blood volume and blood pressure to a normal level, the regulation of these functions either directly or indirectly must be regarded as one of its essential rôles.

On the other hand (table 2), the value of continued treatment with cortical extract during the intervals of comparative well being and adequate

TABLE II
CASES OF ADDISON'S DISEASE TREATED WITH ADRENAL CORTICAL HORMONE
SHOWING IMPROVEMENT

Patient	Age	Sex	Duration of illness before treatment	Duration of treatment	Number of relapses	Blood pressure change	Gain in weight	Present condition	Clinical Diagnosis
D.D.	18	F	5 yrs.	16 mos.	5	none	none	Fair	Tuberculosis
A.O.	61	F	3 yrs.	16 mos.	1	94/68 to 116/82	9.4 kg.	Good	Atrophy(?)
C.G.	29	F	5 mos.	19 mos.	none	none	none	Good	Tuberculosis
C.K.	21	M	14 mos.	12 mos.	1	none	4.4 kg.	Good	Tuberculosis
P.G.	39	M	10 mos.	10 mos.	none	none	2.2 kg.	Fair	Atrophy(?)
R.L.	48	F	9 mos.	4 mos.	1	none	6.5 kg.	Good	Tuberculosis(?)

the recent report of Albright and Baird.³ Our experience leads us to agree with Loeb⁴ in his conception of the Addisonian crisis as a condition of shock, and we believe the value of the usual measures to combat shock and particularly the importance of intravenous saline and glucose solutions is definitely proved. The crisis of Addison's disease is strictly analogous to the condition of insufficiency in the adrenalectomized dog following withdrawal of extract and responds to the same treatment. In all essential particulars they are identical with the condition of shock as seen in both surgical and medical practice. Untreated, death occurs as a result of tissue dehydration, hemoconcentration, and

circulation must be regarded with greater reserve. We have now under observation two patients treated for approximately twenty months. The condition of one of the two is essentially stationary while the other shows slight improvement. Gain in weight has not been striking; no marked change has occurred in the blood pressure, and the pigmentation, while less in amount, is not decidedly improved in either of these patients. Two other cases, both under extract treatment now for about one year, are in very good condition. A comparison of the cases with fatal outcome with those in which more or less improvement has taken place indicates that in the latter group fewer relapses have occurred.

It seems altogether likely that in the prevention or amelioration of repeated relapses by the early use of the cortical extract when symptoms first appear, a definite step may be taken towards the prolongation of life. The average duration of the disease in our group at present under treatment is a little over two years. In a large proportion of cases the disease has an essentially chronic character, although the average duration of life in patients untreated in the large Mayo Clinic group is said to be 16.5 months. Actual prolongation of life therefore has not yet been conclusively demonstrated. It is quite evident that a much greater experience is needed for the proper evaluation of this therapeutic agent upon the eventual course of the disease and its ultimate prognosis.

In determinations of the minimal amounts of extract required for maintenance of the adrenalectomized dog, we have found that the use of certain oils by mouth often permits of lower extract dosage than would otherwise be required. Of the oils so far examined, cotton-seed oil has proved most effective. The action of cotton-seed oil in enhancing the effect of the cortical extract upon the adrenalectomized dog has led us to apply this material to the treatment of our patients with Addison's disease during the intervals of comparatively good condition. We believe that the clinical improvement and absence of relapses under such treatment is sufficiently suggestive to merit further study of its efficacy. The employment of these oils is of little or no value during the relapse, when the extreme nausea and vomiting make their use by mouth very difficult if not impossible. The reasons for the effec-

tiveness of these oils is at present under study. One point only may be observed. The maintenance of good nutrition in the experimental animal is of great importance in lowering the extract requirements. We administer clinically as large doses of the oil as may be tolerated without great distaste, nausea or other undesirable symptoms.

Most important of all as an adjunct to the treatment of the acute relapse with the cortical extract, is the use of large amounts of sodium chloride. If tolerated it should be given by mouth, but it must be administered intravenously and subcutaneously if necessary. Stress must be laid on early treatment. Most patients tolerate well two or three one-gram capsules of sodium chloride when given immediately after the ingestion of food or fluids. Great care must be exercised to avoid increasing the nausea which is inevitably associated with this condition. It is quite definitely shown that patients in relapse usually have marked dehydration and that this underlies the condition of shock. Our unpublished data collected over the past three years, as well as the recently published paper by Loeb⁴ indicates that the acute relapse is characterized by marked loss of sodium and chloride from the blood plasma, and, especially in the earlier stages, increased excretion of these substances in the urine. Even where the plasma chloride content has dropped to 75 mil. eq. per liter (435 mgs. as NaCl per 100 c.c.), sodium and chloride are still excreted in the urine. Further, we have been able to produce an acute relapse in two patients merely by placing them on a salt free diet for four

days. Patients should be cautioned to use ample salt in their diet, and indeed one of our patients (M. S.) particularly craved salt pork, stating that she felt much better when she ate this food.

In conclusion we may summarize our findings as follows: A comparison of the phenomena observed clinically during the relapse of Addison's dis-

conditions in both medical and surgical practice.* It would appear that these are symptoms due primarily or secondarily to a deficient supply of a substance elaborated in the adrenal cortex. (Table 3).

When we come to the maintenance of patients as well as experimental animals not in a condition of shock, however, the points of resemblance are

TABLE III
COMPARISON OF THE PHENOMENA PRESENT IN MEDICAL OR SURGICAL SHOCK, IN THE RELAPSE OF ADDISON'S DISEASE, AND IN ADRENAL INSUFFICIENCY PRODUCED BY WITHDRAWAL OF CORTICAL EXTRACT IN THE ADRENALECTOMIZED ANIMAL

	Medical or Surgical Shock	Relapse in Addison's Disease	Adrenal Insufficiency in the Adrenal- ectomized Dog
Body temperature	Low	Low	Low
Hypotension	Frequently present	Present	Present
Blood non-protein-nitrogen, urea, red cell count, hemoglobin and hematocrit.	Frequent	Common	Present
Pulse	Increased	Increased	Increased
Blood non-protein nitrogen, urea, plasma proteins	Frequently increased	Usually increased	Increased
Nausea, vomiting	Common	Common	Common
Plasma chlorides, bicarbonate, total base and sodium		Low	Low

ease with those of adrenal insufficiency in adrenalectomized dogs after withdrawal of extract, reveals important similarities. The points of resemblance are the extreme muscular weakness, the anorexia, vomiting and diarrhea, the lowered general bodily activity associated with lowered body temperature, blood pressure and general metabolism, the increased concentration of the blood, and finally, the changes in certain chemical constituents of the blood some of which are fairly characteristic of the condition of shock as met with in a variety of pathological

not so striking. Adequate dosage of cortical extract in the dog appears to maintain normal nutrition and weight and to preserve life indefinitely. The blood pressure is normal, there is no hypoglycemia, no increased pigmentation and no change in the basal respiratory metabolism. It has seemed that over a long period of time a moderate grade of secondary anemia develops.

*These changes consist in lowered plasma total base, sodium, bicarbonate, and chloride concentrations. The concentrations of plasma potassium, magnesium, proteins and inorganic phosphate are increased.

In contrast, the patient with advanced Addison's disease, not in relapse, even when given large amounts of a potent preparation of cortical extract continues to exhibit hypotension, usually hypoglycemia, and no striking amelioration in the pigmentation which is characteristic of the disease and without which we are unable to make a diagnosis. The effect on weight and nutrition is variable and sometimes very slight. The basal metabolic rate is lowered in most patients. Well marked anemia is uncommon.

It is a striking fact that the pathological phenomena singularly unaffected by administration of the cortical

hormone in Addison's disease in man, namely, hypotension, hypoglycemia and pigmentation, are just those which do not occur during treated suprarenal deficit in the dog. They are phenomena which a considerable body of experimental evidence associates with disturbance of medullary function and particularly with that of adrenalin. We believe that the evidence is increasing that Addison's disease is probably dependent on disturbed function of both cortex and medulla, and that these two portions of the adrenal gland have reciprocal relations of such a nature that damage to the one produces disturbance of function in the other.

REFERENCES

- ¹CLEGHORN, R. A.: Observations on extracts of beef adrenal cortex and elasmobranch interrenal body, *Jr. Physiol.*, 1932, lxxv, 413.
- ²DUFF, G. L., and BERNSTEIN, C.: Five cases of Addison's disease with so-called atrophy of the adrenal cortex, *Bull. Johns Hopkins Hosp.*, 1933, lii, 67.
- ³ALBRIGHT, F., and BAIRD, P. C., JR.: Treatment of Addison's disease with cortin, *Arch. Int. Med.*, 1932, 1, 394.
- ⁴LOEB, R. F.: Chemical changes in the blood in Addison's disease, *Science*, 1932, lxxvi, 420.

The Influence of Age in the Experimental Production of Hypertrophic Arthritis*

Preliminary Report

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IN a previous communication, evidence has been adduced by the present writers which indicates that it is possible to induce an overgrowth in the patella of dogs, characteristic of hypertrophic arthritis, by ligation of the blood supply to that structure. The changes resulting consisted in a marked increase in size of the patella which reached its maximum about nine months after operation. Control experiments showed that this result was not due to the trauma of operative procedure. The phenomena accompanying overgrowth were essentially those seen in human beings, but there were also some evidences of atrophic arthritis, such as slight erosion or rarefaction of the margins of the patella together with general thickening and adhesions of the soft structures of the joint as a whole, making dissection difficult.¹

Following increasing recognition of the two main types of arthritis first emphasized in this country by Nichols and Richardson² in their classic monograph, studies have been conducted by many workers, having for their aim determination of the etiology of the two types of the disease. These studies have usually indicated, with some exceptions, that arthritis constitutes a syndrome having diversified pathologic manifestations and many etiologic factors. This point of view is that which Nichols and Richardson endeavored to establish, although a few subsequent workers have held a rather more dogmatic attitude which regards the two types of the disease as wholly distinct and referable to quite different etiologic causes. Supporting evidence for the former view is found in the accepted etiologic importance in both types of the disease of such factors as heredity, bodily configuration, imbalance of the nervous system, and dysfunction of the gastrointestinal tract, as well as in the common response of these types to certain forms of therapy. Focal infection, which has long and properly been emphasized, is now regarded as constituting often a precipitating or additional factor only, and one which, although contributory to poor health, may, even when demonstrably present, have little or nothing to do with the actual arthritic process. The most significant advances recently made in

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treatment center around this broader appreciation of the subject.

Notwithstanding this widened outlook, there is avowedly much to be determined as to the extent to which the two types of arthritis, atrophic and hypertrophic, overlap; the extent to which they constitute separate processes; and the extent to which they require different forms of therapy. It is accepted that the clinical phenomena of the two types, as well as the osseous picture by X-ray or "en gros", offer sharp contrasts, but some of the considerations enumerated above strongly suggest some commonality of etiology and of certain physiological deviations underlying the disease as a whole. One of the outstanding observations relating to arthritis as seen in the human being is the fact that atrophic arthritis is, by and large, a disease of the first half of life, and hypertrophic arthritis, by and large, is a disease of the latter half of life. There are exceptions to this, in that atrophic arthritis may appear as late as the eighth decade and hypertrophic arthritis may appear early in mid-life, or, according to some recent observations of Matz,³ even earlier. In general, however, any observations of a large series of arthritics will show that atrophic arthritis tends to disappear at an age at which hypertrophic arthritis tends to begin. It is difficult to see why atrophic arthritis should largely leave the stage at mid-life and why hypertrophic arthritis enters it then, unless these disease states reflect or represent in some way different age responses to the exciting factors. The influence of age as a determining factor in disease of those particular expressions which certain morbid proc-

esses or entities take, is illustrated by disease of the pituitary gland which in youth may express itself as gigantism and in the latter decades as acromegaly. Recent observations by Jaffe and Bodansky⁴ have shown that in guinea pigs age determines the response of the animal to parathormone to such an extent that it is possible by means of injections of parathormone to produce osteitis fibrosa cystica in young animals but not at all in old ones. The expression which renal disease takes in the young offers some contrasts to that which is seen in older persons, and certain differences of the same order are to be observed in connection with cardio-vascular pathology. Again, diabetes in the young exhibits some differences as compared with the disease encountered in the more elderly, and much the same comment can be made regarding tuberculosis. It is thus clear that age introduces factors which may importantly condition the final expression of that deviation of physiology which may underlie any large syndrome, and it becomes pertinent to determine if possible the extent to which this is the case in the syndrome of arthritis. Apart from the clearer concept of the disease which would be afforded by observations elucidating this influence, certain definite and important therapeutic procedures would be given greater or less emphasis. If it could be shown that the surface phenomena of atrophic or hypertrophic arthritis are conditioned in part or largely by age, a wider outlook would have to be entertained upon the problem as a whole, and emphasis upon the separate identity of the two types would be more difficult of justification.

In view of the clear-cut results characteristic of hypertrophic arthritis which followed attempts at reproduction of some of the phenomena of arthritis by ligation of the blood supply to the patella of adult dogs, it seemed desirable to repeat these experiments making use of young dogs only. If it were shown that the response of the tissues differed markedly in young and old animals, the implication would be strong that age constitutes a decisive factor in the induction of hypertrophic arthritis. One starting point in the experiments to be cited was the observation that one of the dogs in the first series operated upon presented ununited epiphyses and that

this animal showed after operation less overgrowth of the patella than developed in the other and older dogs. Experiments were accordingly undertaken upon a series of five dogs, the results of which are set forth in the accompanying protocols. Of five experiments, only three were successful; two failed because of the death of the animal or other accident. In view, however, of the long time required to carry through experiments of this nature, in view of the many hazards to which very young dogs are subjected in the course of such experiments, and in view of the fact that upwards of a year must elapse before further data could be forthcoming, it seems justifi-



FIG. 1. Roentgen-Ray of Old Dog.

Normal patella of dog "Wooley".

Patella of dog "Wooley" six months after ligation of the blood supply to it. Note the size of the overgrowth.

able to present in the form of a preliminary report the results obtained to date.

Dog No. 6—"Collie".¹

Dog No. 7—Male mongrel, wire-haired terrier, named "Wire-haired", seven months old, 15 pounds in weight, was operated upon November 4, 1929. The blood supply to the

gen-ray of February 22. Epiphyses are more nearly united.

July 25, 1930. The epiphyses are united; otherwise no change from the roentgen-ray of May 10. (Figure 2)

November 22, 1930. No change from the roentgen-ray of July 25. On November 22, the dog was sacrificed.

Examination after death showed a normal



FIG. 2. Roentgen-Rays of Young Dogs.

Normal patella of dog "Wire-haired".

Patella of dog "Wire-haired", eight and three-quarters months after ligation of its blood supply. Note absence of distal growth.

patella of the right leg was ligated, resulting in lameness of that leg. The lameness almost disappeared in one week.

Roentgen-rays of the leg operated upon on the following dates showed:

October 31, 1929. A normal knee joint, epiphyses not united. The roentgen-ray was taken before operation.

February 22, 1930. A slight change in the shape of the patella. The epiphyses are uniting.

May 10, 1930. No change from the roent-

left leg and patella and a right leg that seemed normal on dissection, had no thickening of the tissues nor adhesions, but that showed a slightly deformed articular surface of the patella. The right patella could be dissected and stripped as easily as a normal patella and it split with as much difficulty. It was smooth and shiny on its articular surface, but slightly livid in color. The sheath of the proximal tendon had grown somewhat down over the patella and up around its sides, almost merging with the articular sur-

face and covering an area of erosion on this articular surface. The patella showed no overgrowth, only a change in shape.

Dog No. 8—A female mongrel fox terrier, named "Pup", four months old, 10 pounds

in weight, was operated upon November 4, 1929. The blood supply to the patella of the right leg was ligated, resulting in lameness of that leg. The lameness almost entirely disappeared in one week. (Figures 3 and 4)



Normal patella of dog "Pup".

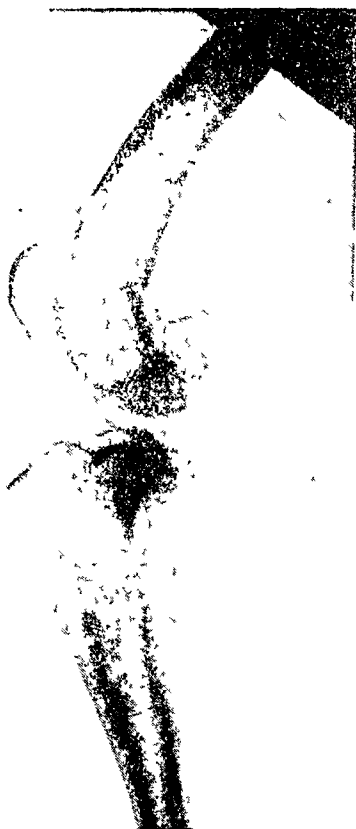


FIG. 3

Patella of dog "Pup" eight and three-quarters months after ligation of its blood supply. Note the spike-like but localized overgrowth distally.

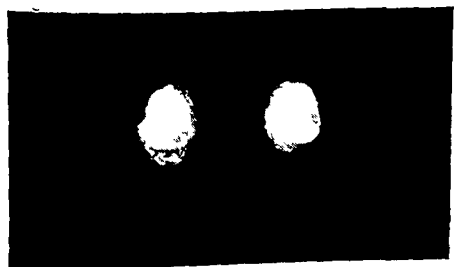


FIG. 4. Photograph of the patellae of dog "Pup" showing overgrowth of the patella on the left, twelve and one-half months after ligation of the blood supply to it. The overgrowth consisted of a spike rather than of the patella as a whole.

Roentgen-rays of the leg operated upon on the following dates showed:

October 31, 1929. A normal knee joint, epiphyses not united. The roentgen-ray was taken before operation.

February 22, 1930. A distal overgrowth, consisting of a spike from the outer edge of the patella.

May 10, 1930. A slight increase in the length of the spike distally, erosion of the patella making the spike appear longer.

July 25, 1930. No change from the roentgen-ray of May 10, except that the epiphyses are almost united.

November 22, 1930. No change from the roentgen-ray of July 25.

On November 22, 1930 the dog was sacrificed

Examination after death showed a normal left leg and patella. The right leg dissected out normally; it showed no thickening of the tissues and only slight adhesions above the patella. There was, however, an area of erosion on the left side of the condyle of the femur at the knee joint. The right patel-

and giving the overgrowth a shelf-like appearance, and adding to its apparent length.

Dog No. 17—A female mongrel fox terrier, named "Cleo", five months of age, 15 pounds in weight, was operated upon September 1, 1931. The blood supply to the patella of the left leg was ligated, resulting in lameness of that leg. (Figures 5 and 6)

Roentgen-rays of the leg operated upon on the following dates showed:

July 26, 1931. A normal knee joint, epiph-

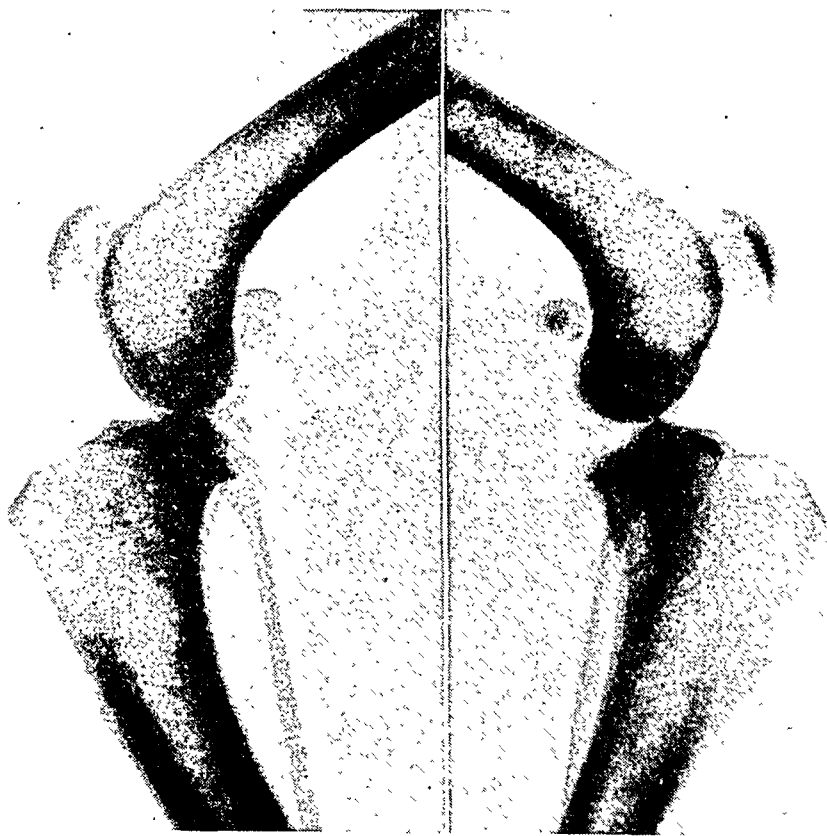


FIG. 5

Normal patella of dog "Cleo".

Patella of dog "Cleo" nine months after ligation of its blood supply. Note the very slight overgrowth distally.

la dissected out easily, but was slightly more difficult to strip than the normal one. The articular surface was smooth and glistening, but at least one millimeter shorter than the normal one. The right patella itself showed an overgrowth of about one millimeter, but only of the part of the patella that adhered to the tendon. There were areas of erosion under the articular surface of the patella, the one at the distal end being the largest

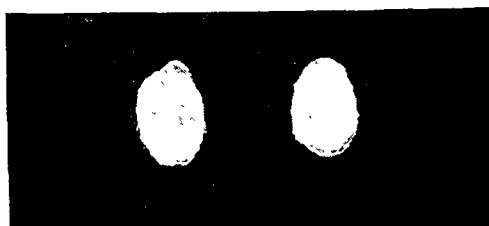


FIG. 6. Photograph of the patellae of dog "Cleo" showing overgrowth of the patella on the right, nine months after ligation of the blood supply to it.

yses not united. The roentgen-ray was taken before the operation.

October 24, 1931. No change from the roentgen-ray of July 26.

January 29, 1932. Epiphyses almost united, otherwise no change from the roentgen-ray of July 26, 1931.

February 8, 1932. No change from the roentgen-ray of January 29.

June 23, 1932. A very slight overgrowth distally, epiphyses united.

On July 8, 1932 the dog was sacrificed.

Examination after death showed a normal right leg and patella and a left leg that seemed normal on dissection, showed no tissue thickening and only slight adhesions around the patella. Both patellae were equally difficult to dissect free and strip. The left patella showed a slight overgrowth distally of the whole patella of about one millimeter (7 per cent). There were also places on the non-articular surface of the left patella that had remnants of suture material imbedded.

Dog No. 20—A female mongrel fox terrier, named "Spotty", three months of age, 8 pounds in weight, was operated upon February 19, 1932. The blood supply to the patella of the left leg was ligated, resulting in lameness of that leg.

Roentgen-rays of the leg operated upon on the following dates showed:

February 8, 1932. A normal knee joint, epiphyses not united. The roentgen-ray was taken before operation.

July 1, 1932 (after death). No change from the roentgen-ray of February 8.

On April 7, 1932, she died of an infection due to a cystic calculus.

Examination after death showed a normal right leg and patella, the epiphyses not united, and a left leg that dissected out easily, showing no tissue thickening and no adhesions around the patella. The left knee joint showed some discoloration due probably to hemorrhage following the operation; also its epiphyses were not yet united. The left patella showed no overgrowth. Both patellae split with slight difficulty and showed inside a brownish coloration of the bone, which was slightly larger in area in the normal patella. Both patellae stripped very easily.

A review of the above protocols shows that a difference apparently exists between the response of older dogs subjected to ligation of blood supply to the patella and that of younger animals chosen before union of the epiphyses. While some overgrowth of the patella may occur, in none of the three young dogs carried along for ten months or a year was there an overgrowth strictly comparable to that seen in all of the older animals; and in two of the young dogs the overgrowth was practically negligible or not to be detected at all.

It has been suspected by some students of arthritis that hypertrophic arthritis appears at mid-life because of the differing response of the tissues consequent upon some factor such as arteriosclerosis, or its vascular precursors, which is present in greater or less degree in all humans or animals that reach that age. In the three experiments just detailed there is a definite suggestion that prior to the appearance of the vascular or other changes of maturity, the end result falls short of the frank picture which is seen in the older animals.

The influence of age upon the type of arthritis cannot be regarded as settled on the basis of one line of experimentation, but one inference that may be drawn is that the phenomena of hypertrophic arthritis may represent a response due to the particular condition of the tissues rather than the effect produced by the action of any type-specific etiologic factor.

This general deduction must be correlated with the evidence that a number of factors often underlie both types of the disease, etiologically and therapeutic.

tically. As already mentioned, some of these factors in human beings are the influence of heredity, the bodily configuration, imbalance of the nervous system, a condition resembling vasoconstriction at the periphery, anatomical and physiological deviations of the gastrointestinal tract, and the influence of a balanced but restricted dietary.^{5,6}

To this list might be added the influence of focal infection though some observers believe that infection has no relation to hypertrophic arthritis. Final proof of this is difficult, however; and it is probable that most dispassionate students regard focal infection as at least contributory to the syndrome of hypertrophic arthritis, although having less obvious and flagrant consequences than in atrophic arthritis.

To these considerations must be added the further fact that there is present in ossifying tissue, though only in

traces in unossified cartilage, the enzyme phosphoric esterase shown by Robison⁷ to be concerned in the formation of bone.

SUMMARY

Preliminary report is made of experiments in which the attempt to produce hypertrophic arthritis in young dogs by curtailment of the blood supply to the patella is accompanied by slight or negative results as compared with similar attempts carried out upon mature animals. Taken in conjunction with other data the observations here cited seem, so far as they go, to add cogency to the view that hypertrophic arthritis is, in part at least, a function of the kind of response which the more adult tissues yield rather than exclusively a response to distinct etiologic factors basically different from those which are present in atrophic arthritis.

REFERENCES

- ¹GOLDHAFT, A. D., WRIGHT, L. M., and PEMBERTON, R.: Production of hypertrophic arthritis by interference with blood supply, *Am. Jr. Med. Sci.*, 1930, clxxx, 386-397.
- ²NICHOLS, E. H., and RICHARDSON, F. L.: Arthritis deformans, *Jr. Med. Res.*, 1909-1910, xxi, 149-221.
- ³MATZ, P. B.: Clinical and economic factors of arthritis in 450 ex-members of the military service, May 9, 1932, Conference on Rheumatic Diseases, The American Committee for the Control of Rheumatism, New Orleans, La. (Address: Washington, D. C.)
- ⁴JAFFE, H. L., BODANSKY, A., and BLAIR, J. E.: The sites of decalcification and of bone lesions in experimental hyperparathyroidism, *Arch. Path.*, 1931, xii, 715-728.
- ⁵RHEUMATISM PRIMER, American Committee for the Control of Rheumatism. Preliminary printing, 1932.
- ⁶MINOT, G. R.: Chronic arthritis; remarks concerning prevention and treatment, *Med. Clin. N. Am.*, 1932, xv, 797-804.
- ⁷MARTLAND, M., and ROBISON, R.: Preparation and use of bone phosphate, *Biochem. Jr.*, 1929, xxiii, 237-242.

A Correlation of the Hemodynamics, Function, and Histologic Structure of the Kidney in Malignant Arterial Hypertension with Malignant Nephrosclerosis*†

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THE correlation of the functional behavior and the structural characteristics of the blood vessels with the physiological units of the kidney is one of the most significant advances in the knowledge of kidney diseases during the past two decades. Evidence is accumulating that in the majority of instances of bilateral kidney disease of adult life the failure of the kidney function depends on a primary disease of the renal blood vessels. These cases are now variously classified as hypertensive renal disease, benign or malignant nephrosclerosis, and arteriosclerotic kidney disease. Contrariwise, in acute and chronic glomerulonephritis an "infectious process" is believed to involve primarily the glomeruli and tubules. The pathological state of the blood vessels in these latter cases, particularly in chronic glomerulonephritis, also plays a significant rôle in the mechanism of disturbed kidney function.

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In this rather simple but somewhat arbitrary grouping of bilateral kidney diseases, the classification of malignant nephrosclerosis is particularly difficult. Volhard and Fahr,¹ and Löhlein² separated this condition from the larger group of glomerulonephritis on the basis of the age of the patients, the rapidly fatal course, certain laboratory findings, and the "acute" histological changes in the glomeruli. The infectious character of the glomerular lesions was emphasized by Volhard and Fahr without sufficient consideration of the vascular lesions. Recently, through the efforts of Fahr,³ the significance of the necrotizing arteriolitis, productive endarteritis and periarteritis of the kidneys and other organs has been receiving a new interpretation. He believes that the glomerular changes, which often predominate in the histologic picture, represent secondary effects of prolonged ischemia produced by vascular damage. Löhlein,² Jores,⁴ Bell and Clawson,⁵ and Shapiro⁶ have claimed that the fundamental mechanism of benign and malignant nephro-

sclerosis is of identical nature, and that these conditions differ only in the rate of their development. These authors believe that the more rapid decrease in the blood supply in malignant nephrosclerosis results in glomerular ischemia and in more acute histological changes resembling those of an infectious process. Stern,⁷ Fishberg,⁸ Murphy and Grill⁹ also agree that both benign and malignant nephrosclerosis are due to vascular sclerosis.

Volhard¹⁰ in 1923 relinquished his toxic theory of the etiology of malignant nephrosclerosis and attributed the histological changes to a general vasoconstriction associated with an intense capillary spasm of the glomeruli. According to him, the capillary ischemia thus caused tends to produce degenerative and proliferative changes. This concept was rejected recently by Klemperer and Otani,¹¹ who pointed out that if in the pathogenesis of this condition the capillary system were the seat of primary disturbance, the changes should be distal to the glomeruli, whereas in reality the vascular changes lie in the afferent arterioles as well as in the glomeruli. They traced the origin of the glomerular changes to thrombotic or proliferative occlusion at some point in the afferent arterioles. Meyer-Stettin,¹² Sternberg,¹³ Ask-Upmark,¹⁴ and others have, on the other hand, brought forward evidence against the identical sclerotic character of benign and malignant nephrosclerosis. It is evident, then, that at present a detailed interpretation of the changes in the blood vessels and in the kidney units in malignant nephrosclerosis is not possible.

An unusual coincidence of events,

to be described below, has permitted us to conduct observations on malignant nephrosclerosis which allow for the first time a correlation between the hemodynamics of renal circulation and the structure of the blood vessels and the function and structure of the kidney. Some data concerning the natural history of the disease have also been obtained. Below we present the clinical course of the disease as observed in a patient, followed by functional and histological studies.

I. CLINICAL COURSE

R. J. W., a 27-year-old male white truck driver, was admitted to the hospital November 16, 1930. His *chief complaint* was "blood in the urine". He was "in perfect health" until six months previously when he experienced hematuria, abdominal discomfort, and blurring of vision.

The hematuria occurred at first about every two weeks and lasted for about a day. These attacks gradually increased in frequency, intensity and duration until two months before entrance to the hospital. Since then hematuria had been continuous but with changing severity. No retention or incontinence of urine, chills, fever, or edema was observed. The abdominal discomfort was generalized, rather constant, and of mild degree. Heat, rubbing and simple medications did not relieve the pain. Blurring of vision was rather diffuse. In addition to these three main symptoms, he also suffered from headache, nausea, and vomiting, which were attributed by the patient to the consumption of alcohol. He had been a heavy drinker for the past three to four years. He claimed some correlation between alcoholic debauches and renal hemorrhages.

Dyspnea, experienced on moderate exertion, developed six months previous to admission. Periods of palpitation lasting 10 to 15 minutes had been occasionally observed. No other noteworthy changes in the function of organs were noticed.

The patient had suffered in the past from infrequent attacks of tonsillitis. The history

as to other infections was essentially negative with the exception of the occurrence of gonorrhea. His mental makeup was natural. No history of familial diseases was obtained.

Because of the free unilateral renal bleeding observed during cystoscopy, and because of certain changes in the roentgen-ray shadow of the kidney pelvis, a surgeon had been led to inform the patient of the possible existence of a malignant tumor of the left kidney. Following an attack of profuse

hematuria, the patient was rushed to the hospital for an immediate nephrectomy.

A left-sided nephrectomy under novocaine spinal anesthesia was performed November 18, 1930. The observations made during this operation will be reported further on.

The *physical examination* the day following the nephrectomy revealed a rather thin, ivory pale adult with prominent shiny eyes, comfortably lying flat in bed. The pupils reacted normally. The ocular fundi were



FIG. 1. Cortical surface of the left kidney removed surgically. Numerous small sub-surface hemorrhages are visible. X 1.3.

edematous with swelling of both discs and pronounced blurring of the margins. Numerous small, irregularly shaped, whitish areas were visible over both retinas. The small arteries were narrow and both these

any evidence of engorgement. The thyroid gland was not palpable. The superficial veins of the upper chest anteriorly were somewhat dilated. The lungs were normal. The apex beat of the heart in the fifth costal interspace was



FIG. 2. Surface of the longitudinal cross section of left kidney removed surgically. Scattered minute hemorrhagic areas. X 1.3.

and the small branches of the veins were tortuous. Arterial compression of the large veins was observed. The mucous membranes of the mouth were rather pale. The tonsils were small and innocent in appearance. No exudate could be squeezed out. The veins of the neck showed normal pulsations without

rather prominent. The maximal left diameter of the heart was only 10 cm. in the fifth interspace. The entire precordium was elevated through the force of the systolic impulse of the heart. The first heart sound was of normal intensity and quality and was continued by a short high-pitched systolic

murmur over the apex. The second sound over the apex was loud. At the base there was a reduplication of the second sound. The aortic second sound was metallic in character and loud. The heart rate was regular. The radial pulse was small, well sustained, and forceful. There was no evidence of arteriosclerosis. The arterial blood pressure was 185 mm. of mercury systolic and 120 mm. diastolic. The abdomen showed some resistance. No organs were palpable. There was a very slight cyanotic pallor of the nail beds of the fingers. The extremities, otherwise, were negative. The neurological examination revealed no abnormal signs. The rectal temperature was normal. The specific gravity of the urine was 1.008. The blood contained 3,330,000 red blood cells and 15,000 leukocytes per cu. mm. with 70 per cent hemoglobin. The diagnosis following operation was *malignant hypertension with nephrosclerosis*.

It is of interest that the first specimen of urine obtained following operation, contrary to the one obtained before, was free of blood. The chemistry of the blood and the kidney function tests, however, indicated for about two weeks after operation a progressive impairment of the kidney function. The urea clearance test reached as low a level as 3.4 c.c., or 6.4 per cent of the average normal clearance with a blood urea content of 142 mg. per 100 c.c.; and the creatinine clearance 8.1 c.c. of filtrate of urine with 11.6 mg. of creatinine in 100 c.c. of blood. Simultaneously with these changes the blood pressure rose to 200 mm. of mercury systolic and 130 mm. diastolic. The degree of edema of the retinal discs increased. Nausea and vomiting were occasionally present. The patient received a diet containing 20 gm. of protein with an adequate caloric content. The fluid intake was liberal. From the seventeenth day after the operation onward the kidney function showed progressive improvement and simultaneously the patient felt very much better. The appetite became voracious. The edema of the optic discs decreased. Toward the end of December his general condition was excellent and the blood urea fell as low as 47 mg. per 100 c.c. of blood.

Beginning soon thereafter, however, the blood pressure rose again to from 200 to 210

mm. of mercury systolic and 130 mm. diastolic. This was followed in four days by severe headaches, puffiness about the eyes and a decrease in the functional capacity of the kidney with unchanged urinary sediment. On January 8th headache was intense, and nausea and vomiting were also present. No explanation could be found for this attack of cerebral vascular crisis, which could not be relieved with luminal and pyramidon. The next day the manifestations of the cerebral crisis improved except for the facial edema. The following night a severe attack of cough and dyspnea developed. The patient sat up in distress and raised frothy blood-tinged sputum. This, together with the moist râles heard over the entire chest, suggested an attack of "paroxysmal nocturnal dyspnea" (cardiac asthma) with pulmonary edema. Morphine (gr. 1/4) and atropine (gr. 1/60) relieved this distress promptly, and in the morning the patient felt comfortable. There was, however, impaired resonance of mild degree over the right side of the chest anteriorly and posteriorly with somewhat decreased excursion of the diaphragm. The breath sounds were diminished and there was an increase in the spoken voice and fremitus. The arterial blood pressure was 200 mm. of mercury systolic and 130 mm. diastolic; the vital capacity of the lungs was 4200 c.c. The liver and spleen were not palpated and ascites and edema were not observed.

In the evening of January 11th we had another opportunity to observe in detail the development of paroxysmal nocturnal dyspnea. The patient ate a good supper and was comfortable. At about 8 p.m. he felt a tight sensation beneath the manubrium sterni. He became restless and complained of inspiratory difficulty. The right side of the thorax now showed limited excursion with a few fine and medium consonating râles over that side. The arterial blood pressure was 205 mm. of mercury systolic and 136 mm. diastolic, the venous blood pressure 12 cm. of water. The condition grew rapidly worse. The patient was pale and cold and covered with sweat. The "tightness in the chest" and the dyspnea became so severe that a marked degree of orthopnea developed. There was extreme apprehension of death. The pa-

tient coughed with considerable distress, raising red frothy sputum with occasional red streaks of blood. The heart sounds became rapid, and while before the attack the aortic second sound was loud and metallic, now the relationship changed and the pulmonary second sound became accentuated and louder than the aortic second sound. There was at the same time an almost complete fixation of the right side of the thorax with dullness and a definite increase in the intercostal retraction. The breath sounds were almost completely absent but numerous fine, medium and coarse râles were heard throughout the right lung. *While these physical signs indicated severe changes in the right lung, the physical signs of the left side of the chest remained essentially normal.* The heart rate rose to 150 per minute. The arterial blood pressure was 225 mm. of mercury systolic and 140 mm. diastolic.

Morphine (gr. 1/4) failed to give any relief. Blood pressure cuffs were then applied on the proximal end of the four extremities and the pressure was raised in each to the level of the diastolic blood pressure. Within one minute after the application of venous stasis the dyspnea, cough, and raising of sputum disappeared and the patient fell asleep. On relieving the pressure in the cuffs temporarily at ten-minute intervals, all the symptoms and signs returned though with decreasing intensity. After one hour the cuffs were removed and the patient remained comfortable. Physical examination now was essentially the same as before the attack. The loud metallic quality of the aortic second sound returned and the accentuation of the pulmonary second sound subsided. The patient was given tincture of digitalis in an amount equivalent to 2 minims per pound of body weight. Next day the patient was comfortable. The breath sounds were somewhat reduced over the right side. A few days later the patient suffered again from a similar attack of paroxysmal dyspnea. Between attacks, Cheyne-Stokes' type of breathing developed, with a sense of suffocation toward the end of the apneic stage. Intravenous administration, slowly, of 50 per cent glucose solution gave considerable relief for six hours. Ten days after the first attack of dyspnea, or on January 19th, the

patient appeared exhausted, and involuntary jerky movements of the extremities developed; Cheyne-Stokes' breathing was now marked with prolonged apnea and a protodiastolic gallop rhythm appeared. The pulmonary second sound became persistently louder than the aortic second sound. Râles were heard over the chest. The liver edge was 6 cm. below the costal margin. In order to relieve the manifestations of uremia a lumbar puncture was performed. The spinal fluid pressure was 280 to 320 mm. of water. The dynamics and oscillations of the fluid were normal. The intraspinal injection of 20 c.c. of a 10 per cent magnesium sulfate solution caused a temporary drop of fluid pressure to 200 followed by a rise to 280 mm. of water. Inhalation of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen gave relief from the irregular periodic breathing. The patient during the following two days became more drowsy. There was increasing edema of the eyegrounds and the veins of the discs were more congested. A pericardial friction rub appeared. The blood pressure was 190 mm. of mercury systolic and 120 mm. diastolic, the pulse 130 per minute. The spinal fluid pressure January 19th was 350 mm. of water with normal dynamics. On January 20th the patient was very stuporous. The pulmonary edema disappeared although the general condition grew worse. On January 22nd the pericardial friction rub persisted. He was now growing weaker, although the blood pressure was still maintained as high as 180 mm. of mercury systolic and 120 mm. diastolic. The pulse was 136 per minute. Next day he was comatose, the blood pressure was 175 mm. of mercury systolic and 100 mm. diastolic, pulse 136. He died January 24th.

Obviously the left kidney of this patient was removed because of a mistaken diagnosis and because of the alarming unilateral renal bleeding. Considering that the patient had experienced six months previous to his admission such symptoms as hematuria, abdominal discomfort and blurring of vision, and considering that he lived two months after the operation, it may

be concluded that the course of this rapidly fatal disease was not significantly shortened in his case by the nephrectomy.

Attacks of paroxysmal dyspnea, such as this patient experienced, are not rare in malignant hypertension. They develop often independently of the kidney involvement, usually at an early stage of relative failure of the left ventricle. One of us (S.W.) has observed attacks of paroxysmal dyspnea in a child eight years old with malignant hypertension who died as a result of heart failure while still retaining normal kidney function. The changes in the clinical symptoms and signs which occurred during attacks in the case recorded in detail above, have been observed by us in a number of other similar cases. They depend on the circulatory changes, which, together with therapeutic measures in this syndrome, have been previously summarized.¹⁵

II. FUNCTIONAL STUDIES

The Hemodynamics of the Normal Kidney and of the Kidney with Malignant Nephrosclerosis. If the human kidney is exposed surgically, blood from the renal vein can be obtained easily under sterile conditions and with apparent safety. In puncturing the vein it is essential that no more than gentle traction be made upon the kidney, so as not to interfere with the normal free flow of the blood. We have punctured the renal vein in five cases without any resultant bleeding. The composition of the arterial blood throughout the body is identical so that if simultaneously with obtaining blood from the renal vein blood is collected from the femoral artery and the specimens studied chemically, information

can be obtained concerning the blood flow through the kidneys. Table 1 presents the results of such observations on the oxygen and carbon dioxide content of the blood, obtained under oil, from the patient with malignant hypertension and nephrosclerosis and from three individuals with normal kidney function who had one kidney exposed for surgical suspension. The 10 to 20 c.c. of renal vein blood were drawn slowly during a period of from two to three minutes so as to represent a sample of a relatively large amount of blood flowing through the kidney. In addition to obtaining blood from an artery and from the renal vein, blood was also obtained from the femoral vein in order to form a comparative estimate of the blood flow through the kidney and through a lower extremity. In order to ascertain whether or not spinal anesthesia exerts an influence on the blood flow, in two of the control cases and in the patient with nephrosclerosis, blood was obtained from the femoral vein during anesthesia and again after the effect of the anesthetic wore off. Obviously if the metabolism of an organ remains unaltered or becomes increased, a decreased oxygen difference between the arterial and venous blood indicates an increased blood flow. The data given in table 1 demonstrate that the oxygen difference between the bloods obtained from the femoral arteries and veins with and without anesthesia was essentially unaltered in the patient with hypertension, while it was increased definitely in one, and essentially unaltered in the second control "normal" cases. The arterial blood pressure was distinctly lower during the spinal anesthesia in the patient with nephrosclerosis, but it

TABLE I
BLOOD GAS STUDIES OF THE KIDNEY AND LEG IN THE CASE OF MALIGNANT NEPHROSCLEROSIS COMPARED WITH NORMAL SUBJECTS

BLOOD GAS STUDIES OF THE KIDNEY AND LEG IN THE CAT

Name	Age	Condition of Kidneys	Arterial Blood Pressure		Heart Rate	Femoral Artery				Femoral Vein		Renal Vein		Femoral Arter.-Ven. Difference		Renal Arter.-Ven. Difference		Remarks
			Syst.	Diast.		O ₂ Content	Vol. %	O ₂ Saturation	CO ₂ Content	O ₂ Content	CO ₂ Content	O ₂ Content	CO ₂ Content	O ₂	CO ₂	O ₂	CO ₂	
			mm. Hg	mm. Hg	per min.	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	
R.W.	27	Malignant Nephro-sclerosis, impaired	220	130	108	10.58	12.01	88	52.12	5.98	56.76	—	—	4.60	4.64	—	—	Before spinal anesthesia
R.W.	27	Malignant Nephro-sclerosis, impaired	110-140	75-100	88	11.17	11.97	93	49.16	7.72	53.46	11.32	50.45	4.45	4.30	-0.15	1.29	During spinal anesthesia
A.B.	47	Normal	115	70	68	—	—	—	—	14.29	53.92	—	—	4.93*	6.26*	—	—	Before spinal anesthesia
A.B.	47	Normal	120	85	68	19.21	20.04	96	47.66	14.41	54.83	16.34	50.45	4.80	7.17	2.87	2.79	During spinal anesthesia
R.B.	45	Normal	120	60	80	18.20	18.84	—	46.20	12.14	52.28	—	—	6.06	6.08	—	—	Before spinal anesthesia
R.B.	45	Normal	105	62	75	18.46	19.00	—	45.00	14.60	49.90	15.50	49.28	3.86	3.90	2.96	4.28	During spinal anesthesia
D.K.	40	Normal	110	60	78	16.25	16.79	97	37.14	8.93	43.93	14.96	42.03	7.32	6.79	1.29	4.89	During spinal anesthesia

*Assuming that the gaseous content of the blood from the femoral artery is the same before and during spinal anesthesia.

did not change appreciably in the control cases. The most significant observation is, however, the low oxygen difference between the blood from the renal artery and vein in the control cases. This, in view of the fact that the metabolism of the kidney as compared with other organs is high, corresponding to 8.2 per cent of the total energy consumption in rats, and 7.9 per cent in dogs,^{16,21} conclusively indicates the existence of a rapid blood flow through the kidney. The average oxygen difference between the arterial and venous blood of the kidneys of the control subjects was 2.37 vol. per cent. The arterial blood, therefore, lost an average of 13 per cent of its oxygen content during its passage through the kidney. Rhoads, Van Slyke, Hiller and Alving¹⁷ reported that the proportion of oxygen removed from the blood by the kidney of the dog was 10 to 20 per cent of the arterial oxygen content. This indicates a fair degree of agreement between the rapid blood flow through the kidney of the dog and of man. In all three normal kidneys the arteriovenous oxygen difference was distinctly less in the kidney than in the lower extremities.

In the case of the patient with ne-

phrosclerosis, there was no apparent utilization of oxygen by the kidney. On the contrary, the oxygen content of the blood obtained from the renal vein was slightly higher. This surprising finding of somewhat higher blood oxygen content in the renal vein cannot be attributed to technical error in the analysis. This belief is supported by the finding of a higher oxygen capacity of the venous blood (12.66 vol. per cent) than of the arterial blood of the kidney (11.97 vol. per cent). Our interpretation is that the rate of blood flow through the kidney in this case was unusually great, even when compared with the relatively rapid renal blood flow in the control cases with normal vascular systems and normal arterial pressures. The slight increase in the oxygen capacity of the blood in the renal vein was probably due to an increased hemoglobin concentration produced by the loss of water content of the blood in its passage of glomerular capillaries. That the data (table 2) were obtained while the kidney was functioning is supported by the fact that the urea and creatinine clearance tests during spinal anesthesia in the control case were essentially normal. In the case of nephrosclerosis these

TABLE II
A COMPARISON OF CHEMICAL CONSTITUENTS OF THE RENAL ARTERIAL AND VENOUS BLOOD
IN THE CASE OF MALIGNANT NEPHROSCLEROSIS AND IN A CONTROL SUBJECT

Condition	Source of Blood Specimen	Non- Protein- Nitrogen	Urea Nitrogen	Crea- tinine	Chlo- rides
		mg./100 c.c.	mg./100 c.c.	mg./100 c.c.	mg./100 c.c.
(Malignant Nephrosclerosis)	Kidney artery	66	36.1	5.2	590
	Kidney vein	58	32.5	4.9	597
(Control)	Kidney artery	—	13.0	1.4	605
	Kidney vein	—	10.0	1.3	611

tests were about the same as the tests obtained five days later under entirely natural conditions (table 3).

The average 2.4 vol. per cent oxygen difference between the blood of the renal artery and vein observed in the three control cases is smaller than that observed in other organs studied in man. Weiss and Lennox observed an oxygen difference of 7.1 vol. per cent between the blood of the cubital arteries and veins of the arm, and in a study of the brain they noted an average difference of 6.2 vol. per cent between the blood of the internal carotid artery and the internal jugular vein.¹⁸ In the leg, Weiss and Ellis observed an oxygen difference of 4.1 vol. per cent between the blood of the femoral artery and vein.¹⁹ In the heart there has been found 5.3 vol. per cent difference between the arterial and venous blood of the ventricles.²⁰

The Chemical Composition of the Arterial and Venous Blood of the Kidney. Table 3 presents data concerning the comparative content of certain constituents of the arterial and venous blood of the kidney. The differences of the values between the arterial and venous blood are exceedingly small. In view of the unusually rapid blood flow through the kidney, such a small loss of waste products during the passage of blood is not surprising. The amount of the chemical substances in the venous blood, with the exception of chlorides, was less than in the arterial blood, although at times the differences fell within the error of the analysis.

Dunn, Kay and Sheehan²³ observed in rabbits that each 100 c.c. of blood containing originally 30.2 mg. of urea

TABLE III
THE UREA AND CREATININE CLEARANCE DURING SPINAL ANESTHESIA IN THE CASE OF MALIGNANT NEPHROSCLEROSIS AND IN A CONTROL SUBJECT

Age	Diagnosis	Heart Rate	Arterial Blood Pressure		Blood Urea Nitrogen	Urine Urea Nitrogen	Urea Clearance		Blood Creatinine	Urine Creatinine	Glomerular Filtrate	Remarks
			Syst.	Diast.			c.c.	Per cent Normal				
		per min.	mm. Hg	mm. Hg	mg./100 c.c.	mg./100 c.c.			mg./100 c.c.	mg./100 c.c.	c.c./min.	
27	Malignant nephrosclerosis	108	110-140	75-100	35.1	344	11	20	5.2	72	19.5	Duration of tests 95' Left nephrectomy
40	Floating kidney	78	110	60	13.0	772	60	111	1.4	103	71.3	Duration of tests 77' Right nephropexy

lost 2.5 mg. in passing through the kidney. Their study, performed under more ideal experimental conditions, is in harmony with our findings in man. It is, however, contrary to the earlier observations of Picard²⁴ in dogs that the urea content of the blood from the renal vein was half that of the blood from the artery. Picard's findings would suggest a blood flow through the human kidney of 150 c.c. per minute, a figure undoubtedly low. Sheehan's recent finding²² in the rabbit would suggest an average corresponding blood flow of 750 c.c. per minute through the kidneys in man which, even if high, is probably close to the actual state of affairs. As the combined weight of the two kidneys in man is only 1 to 240 in proportion to the body weight, the blood flow through the kidney must be great when compared with other organs.

The Secretory Function of the Kidneys. Table 2 presents the urea clearance tests of the kidneys during surgical operation under spinal anesthesia. In the control case, the urea clearance test measured according to the method of Van Slyke was normal. The creatinine clearance was somewhat below the average normal value.

In the case of nephrosclerosis the urea clearance test during operation was 20 per cent of normal. The longer part of this clearance test fell within the period directly after nephrectomy; and since the clearance test five days later showed 13 per cent of normal, the kidneys during the surgical procedure under spinal anesthesia may be regarded as functioning adequately. Table 4 presents the urea and creatinine clearance tests of the right kidney after removal of the left one. During the three months of observation, we

performed on this patient 12 urea clearance tests according to the Van Slyke method,²⁵ and 11 creatinine clearance tests according to Rehberg's method.²⁶ The results of these two tests paralleled each other fairly closely. It is of interest that, in accordance with the history of the case, these tests indicated considerable fluctuations in the functional capacity of the kidney during the period of three months. Following operation the urea nitrogen content of the blood rose from 35 to 143 mg. per 100 c.c. of blood as the clearance dropped from 20 to 6 per cent of the normal. Simultaneously the blood creatinine rose because the glomerular filtrate decreased. With the subsequent improvement in the kidney function the urea clearance rose to 12 per cent, and the creatinine clearance to 15 per cent of the normal value. Following this temporary improvement, the kidney function showed further impairment. When the urea clearance reached about 3 per cent, and the creatinine clearance about 5 per cent of the normal values, clinical manifestations of uremia developed.

Concentration Dilution Tests of Kidney Function. On two occasions, a concentration dilution test was performed on the patient with nephrosclerosis by the method described.²⁷ In order to study the concentration power of the kidney more specifically, in addition to the specific gravity of the urine, the creatinine concentration of the blood and urine were also measured. These data allow the calculation of the concentration index between the blood and the glomerular filtrate. The results of one of these tests are presented in table 5. Obviously the water elimination, as well as the concentra-

TABLE IV
THE UREA AND CREATININE CLEARANCE IN THE CASE OF MALIGNANT NEPHROSCLEROSIS
FOLLOWING LEFT NEPHRECTOMY

Date	Blood Pressure		Heart Rate	Blood Urea Nitrogen	Urea Clearance		Blood Creatinine	Creatinine Clearance
	Syst.	Diast.			c.c.	per cent normal		
	mm.Hg	mm.Hg	per min.	mg./100 c.c.			mg./100 c.c.	c.c. filtrate
1930								
Nov. 20	150	104	116					
Nov. 21	175	105						
Nov. 22	165	125	100					
Nov. 24	175	125	96	83.7	13	17	6.6	10
					5	9		
Nov. 25	185	130	100					
Nov. 27	185	130	84					
Nov. 28	180	120	80	142.7	3	6	10.4	8
					4	7		9
Nov. 29	185	120	80					
Dec. 1	190	130	76	141.5	3	6	11.6	7.3
					3	6		8.9
Dec. 2	185	125	76					
Dec. 3	185	115	84					
Dec. 4	190	110	80					
Dec. 5	180	110	76	119.6	5	9		
					6	8	10.4	10.8
Dec. 6	185	105	76	83.6	6	8	8.3	9.3
					7	9.4		8.5
Dec. 16	165	110	90	66.9	9	11.4	7.5	9.1
					8	11		15.0
Dec. 20	180	106	100					13.0
Dec. 23	180	115	108	52.3	9	12	6.7	14.6
					8	10.5	6.7	14.5
Dec. 27	175	115	96					
Dec. 30	190	125	92	47.3	6	11		
					8	11.2		
1931								
Jan. 2	200	130	96					
Jan. 6	210	130	100	56.0	4	8.5		
					5	10	7.3	14.5
Jan. 8	205	140	100					12.6
Jan. 12	185	110	121	52.0	4	8.5	8.4	6.8
Jan. 14	185	100	120	80.9	3	6.5	12.8	5.1
								3.3
Jan. 15	175	100	120					
Jan. 19				116.1	1	2.4	15.4	5.6
					2	3.5		3.6
Jan. 23				145.0			18.5	

tion capacity of the kidney was seriously impaired. Notwithstanding the ingestion of a large amount of water, the water elimination showed only slight variations. The creatinine concentration index varied between 2.8

and 6.8, while in control subjects under identical conditions it usually reached the levels between 200 and 300. The results of this test indicate that in this case of malignant hypertension with nephrosclerosis both the volume

and the concentration of urine were fixed.

Urinary Sediment. The urinary sediment was studied daily. The most significant observations were the sudden variations from time to time in the number of white and red blood cells as well as in the character of the casts. A sediment with hyaline or granular casts and normal elements changed rapidly within a day or so to a sedi-

Microscopic Examination: There were foci of increased connective tissue infiltrated with many lymphocytes, some plasma cells and large mononuclears. In places, fairly numerous polymorphonuclear neutrophils were present. In such areas of sclerosis the tubules were narrowed. Scattered through the pyramids were numerous foci of hemorrhage, apparently capillary in origin. The glomeruli showed varying degrees of involvement. Some of them were normal, others showed acute lesions and still others more chronic changes. The acute lesions appeared

TABLE V
THE CONCENTRATION-DILUTION AND CREATININE CONCENTRATION INDEX TESTS IN THE
CASE OF MALIGNANT NEPHROSCLEROSIS

Time Interval of Specimen	Urine Volume	Specific Gravity	Urine Creatinine	Blood-Urine Creatinine Concentration Index	Glomerular Filtrate
	c.c.		mg./100 c.c.		c.c./min.
Jan. 1, 8:00 P.M.—	1600	1.008	44.6	4.4	10.6
Jan. 2, 7:00 A.M.					
7:00 A.M.— 8:00 A.M.	95	1.010	48.1	4.8	7.6
8:00 A.M.— 9:00 A.M.	50	1.011	50.0	5.0	4.0
9:00 A.M.—10:00 A.M.	170	1.007	27.8	2.8	7.8
10:00 A.M.—11:00 A.M.	130	1.007	29.2	2.9	6.4
11:00 A.M.— 1:00 P.M.	200	1.009	49.5	4.9	8.3
1:00 P.M.— 3:05 P.M.	170	1.009	65.4	6.5	9.1
3:05 P.M.— 6:00 P.M.	200	1.011	68.0	6.8	7.5
6:00 P.M.— 8:00 P.M.	165	1.011	62.1	6.2	8.7
8:00 P.M.—					
Jan. 3, 8:00 A.M.	1100	1.009	59.2	5.9	8.9

ment rich in red and white blood cells and casts containing red cells. The albumin content of the urine changed from a small to a heavy trace as the disease progressed.

III. STRUCTURAL STUDIES

The kidney removed at operation appeared as follows:

Gross Description: The kidney weighed 213 gm. The capsule stripped easily. The cortex averaged 5.5 mm. in thickness. The cortical tissue was yellowish grey with a waxy texture. The pyramids in the upper pole showed evidence of small hemorrhages. Several of the pyramids had pearly white, diffuse, firm areas in the region of the kidney pelvis. The entire organ appeared to be edematous.

in various forms. The most common was a hyaline droplet degeneration of the tuft and, to some extent, also of the capsular epithelium, associated with a marked proliferation of the epithelium, especially of the capsule. In some instances this lesion involved the whole tuft with obliteration of the capsular space; in others it affected only a portion of the tuft.

The majority of the tufts in these lesions, when stained with Mallory's anilin blue stain (Lee Brown modification),^{28,29} showed a meshwork of intracapillary fibers described by McGregor³⁰ as characteristic of glomerulonephritis. When only a portion of the tuft epithelium was involved, only the loops adjacent to this area showed such changes, the other loops remaining normal (figure 13). Other glomeruli showed necrosis with fibrin formation and infiltration of varying

numbers of polymorphonuclear leukocytes. A less frequent type of lesion was a necrotizing arteriosclerosis with an associated involvement of the glomerulus, accompanied by an infiltration of a considerable number of polymorphonuclear neutrophils. The more chronic changes in the glomeruli consisted

tained hyaline and granular casts and in places masses of red blood corpuscles and also numerous polymorphonuclear neutrophils and some large mononuclears. In view of the large number of leukocytes in the tubules the sections were carefully examined for organisms but none were found.

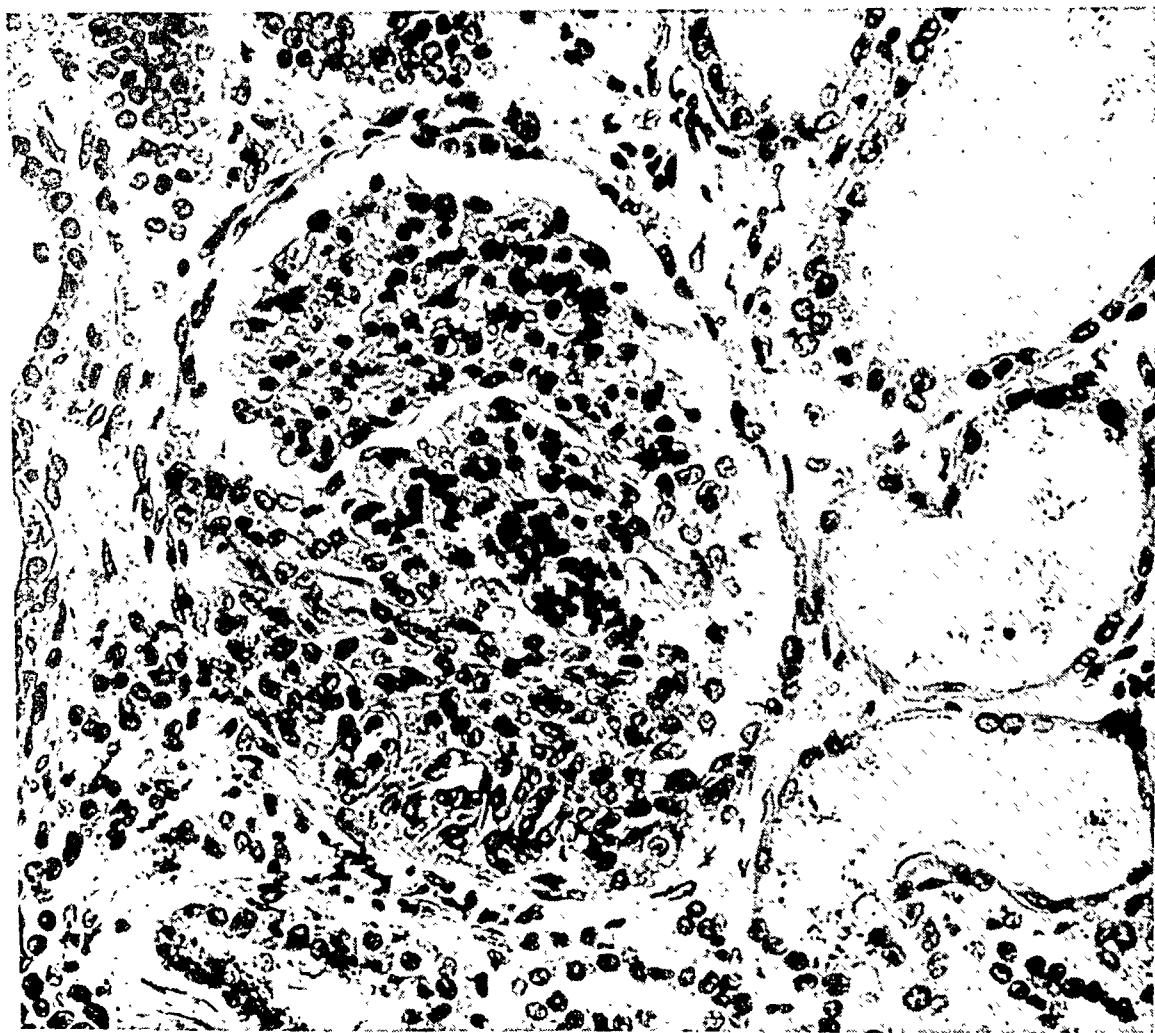


FIG. 13. Right kidney. Glomerulus showing focal lesion with localized reaction on part of epithelium. X 300.

of diminution in size with thickening and wrinkling of the basement membrane, described by McGregor as characteristic of hypertension.³¹ Other glomeruli showed adhesions between the tuft and capsule, and still others were completely sclerosed.

The tubules in the areas showing fibrosis appeared atrophic. Elsewhere the cells of some of them contained hyaline droplets in their cytoplasm; in others the cytoplasm was more granular than normal. The tubules con-

The larger blood vessels showed no pathological changes. Many of the medium-sized and small arteries showed marked fibrous thickening of their walls. Numerous arterioles had thickened, hyaline walls. Some of the smaller arteries and arterioles showed widening of their lumens and necrosis, occasionally with hemorrhage into the surrounding tissue. Fat, demonstrated by staining, occurred especially in the atrophic tubules but was also present in non-atrophic tubules,

artery walls, and glomerular epithelium. Fat also occurred in the casts.

NECROPSY

Gross Description. The autopsy was performed two hours after death by Dr. J. B. Hazard. Only the essential findings are given below.

in thickness. The auricles and the right ventricle were markedly dilated, the ventricle being 0.25 cm. thick. The muscularis was pale red, and of firm consistency with no gross areas of scarring. The endocardium was smooth and all valves were negative. Lungs: Both lungs were enlarged and heavy. Section of the lungs revealed a firm, dark,

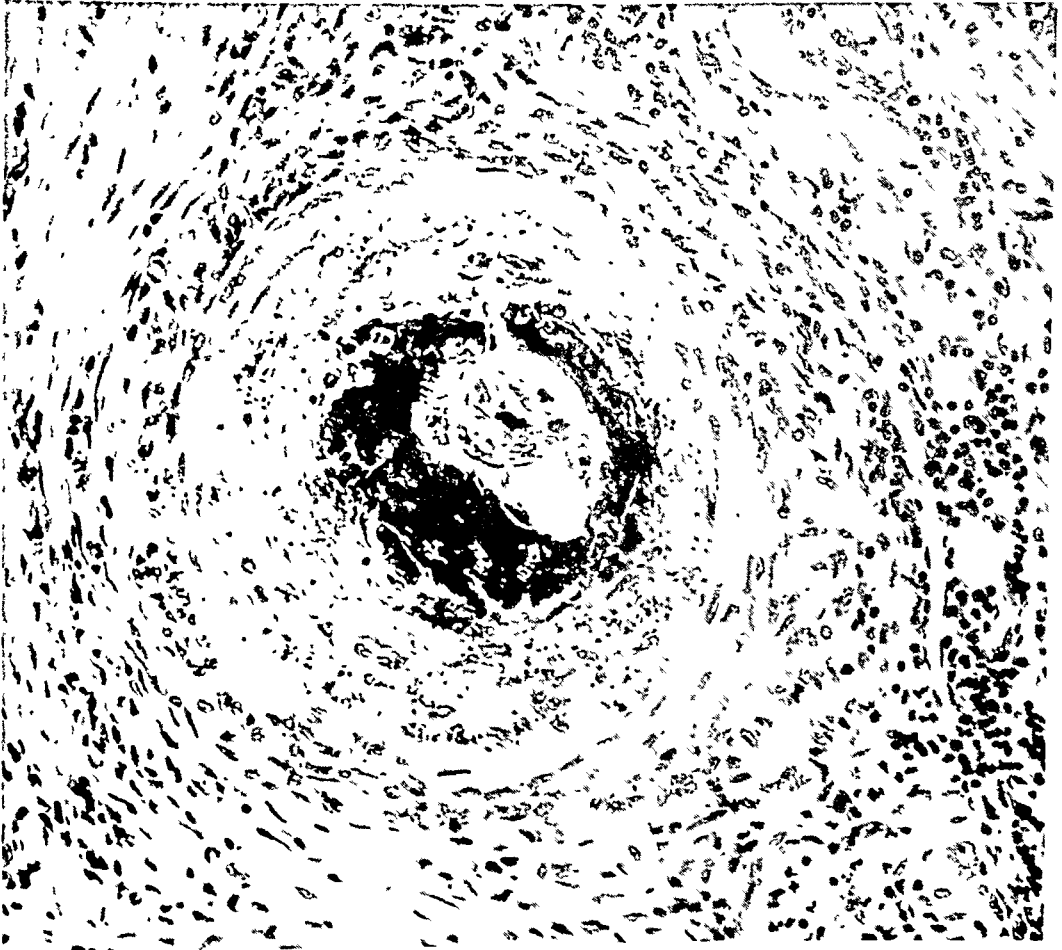


FIG. 15. Pancreas. Artery containing organizing thrombus. Wall degenerating and containing nuclear debris. X 250.

Pleural Cavities: There were about 500 c.c. of clear fluid in the right pleural cavity and 200 c.c. in the left. The surfaces of the cavities were smooth and glistening. **Pericardial Cavity:** Both parietal and visceral pericardial surfaces were covered with a layer of fibrin. About 150 c.c. of clear amber fluid were in the cavity. **Heart:** Weighed 690 gm. The wall of the left ventricle showed marked hypertrophy and measured 2.1 cm.

reddish grey tissue composing all lobes. A quantity of froth and dark red fluid could be expressed. **Liver:** Weight 1930 gm. Section revealed a dark brown tissue of soft consistency with a fine red mottling.

Kidneys: Left kidney was absent. The right kidney weighed 165 gm. The capsule stripped with moderate ease, leaving an irregular pale surface, speckled with many pin point, dark red spots. The cut surface

was pale pink and of soft consistency. In the cortex were several small irregular, red areas measuring up to 0.1 cm. in diameter. The cortex was uniformly thinned, measuring 0.4 cm. in thickness. The pyramids were not remarkable save for their pale color. The pelvis was negative. There was no dilatation of the ureter.

was old and was in the stage of organization. In places the organization process was beginning, in others it was advanced, or complete. This process was taking place, not only in the alveoli but also in the atria and bronchioles. Elsewhere the alveoli were normal or distinctly dilated. The blood vessels appeared normal. Spleen: The germ-

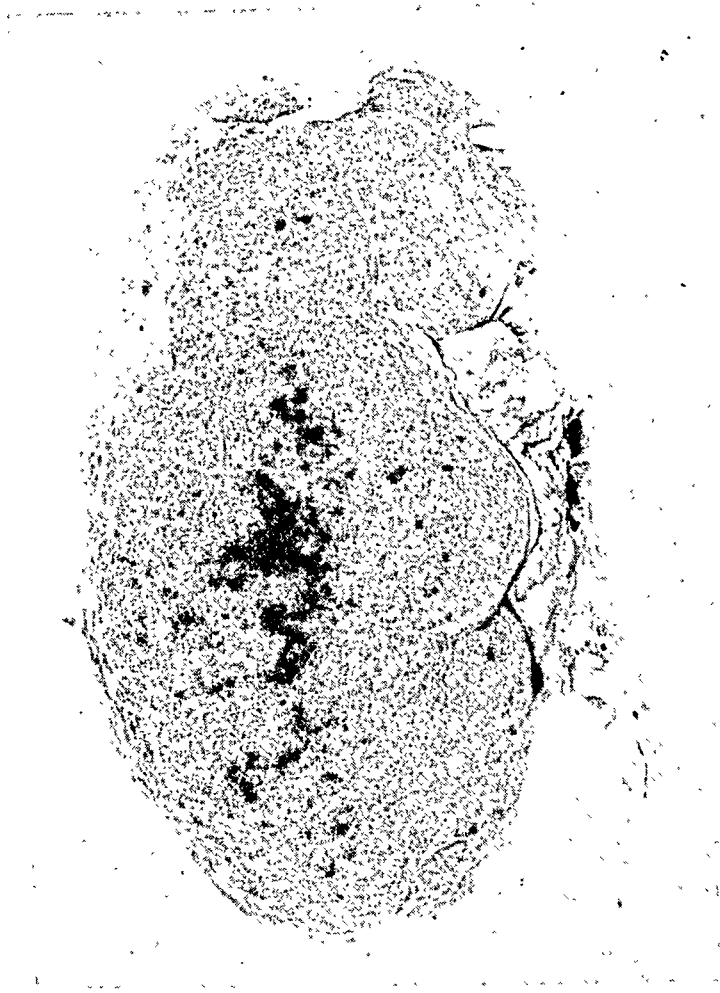


FIG. 3. Cortical surface of the right kidney at necropsy. Numerous small hemorrhages. X 1.3.

Aorta: It appeared smooth and yellowish white throughout. The elasticity was good.

Microscopic Examination. **Heart:** The muscle fibers were increased in thickness. There was a certain amount of lipomatosis and rarely a large mononuclear and mast cell in the connective tissue. The blood vessels appeared normal. The pericardium showed an acute fibrinous pericarditis. **Lungs:** The alveoli contained red blood cells, fibrin, and some large mononuclears. The fibrin

inal centers were not prominent and were inactive. A few contained a hyaline fibrinoid material. The central arteries showed a hyaline thickening of their walls; rarely, there was an infiltration of large mononuclear cells in the wall. The pulp contained numerous polymorphonuclear neutrophils, a considerable number of plasma cells, and a rare megakaryocyte. **Pancreas:** Many of the glands were dilated and contained a pink-staining material, often concentrically arranged, sug-

gesting concretions. In addition, many glands contained polymorphonuclear neutrophiles in their lumens. There was an occasional necrotic acinus invaded by polymorphonuclear leukocytes. The connective tissue stroma was diffusely infiltrated with polymorphonuclear neutrophiles, lymphocytes and large mononuclears. A considerable number of

sis as evidenced by loss of liver cells and sclerosis. In addition, an active, acute central necrosis, in places hemorrhagic in type, was present. An occasional arteriole in the portal areas showed hyaline in its wall.

Right Kidney: There was a marked increase in connective tissue with a moderate infiltration with lymphocytes; these cells

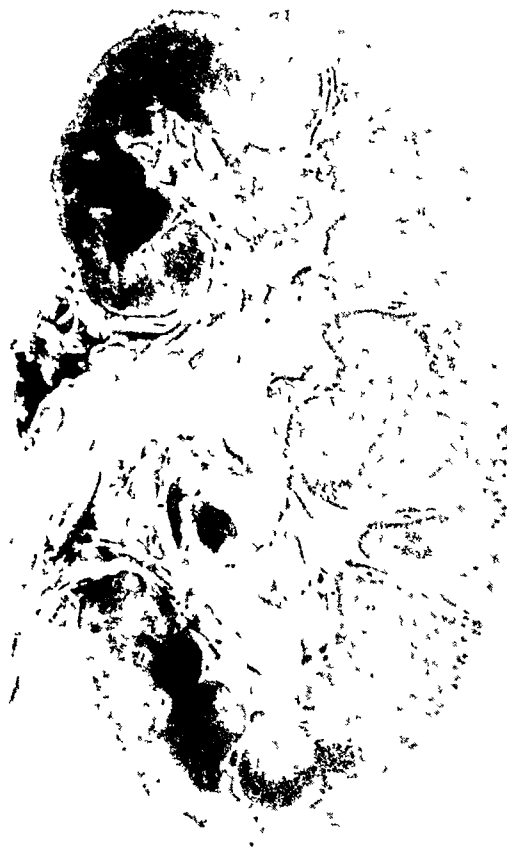


FIG. 4. Surface of the longitudinal cross section of the right kidney at necropsy. Numerous small hemorrhages. X 1.3.

the small arteries and arterioles showed a thickening of their walls, often with a deposit of hyaline. Occasionally one showed necrosis of its thickened wall. Several small arteries contained thrombi partially occluding their lumens. In one such artery (figure 15) the thrombus was undergoing organization while the vessel wall showed necrosis and hemorrhage. Rarely the thickened vessel wall contained fat.

Liver: There was a healed central necro-

were, however, much less numerous than in the kidney removed surgically. The glomeruli showed lesions of both an acute and more chronic nature. There was a considerable number of normal glomeruli. The number of glomeruli showing thickened and wrinkled basement membranes was considerably increased over that in the left kidney removed two months before. The acute changes in part resembled those in the first kidney. They consisted in hyaline droplet degenera-

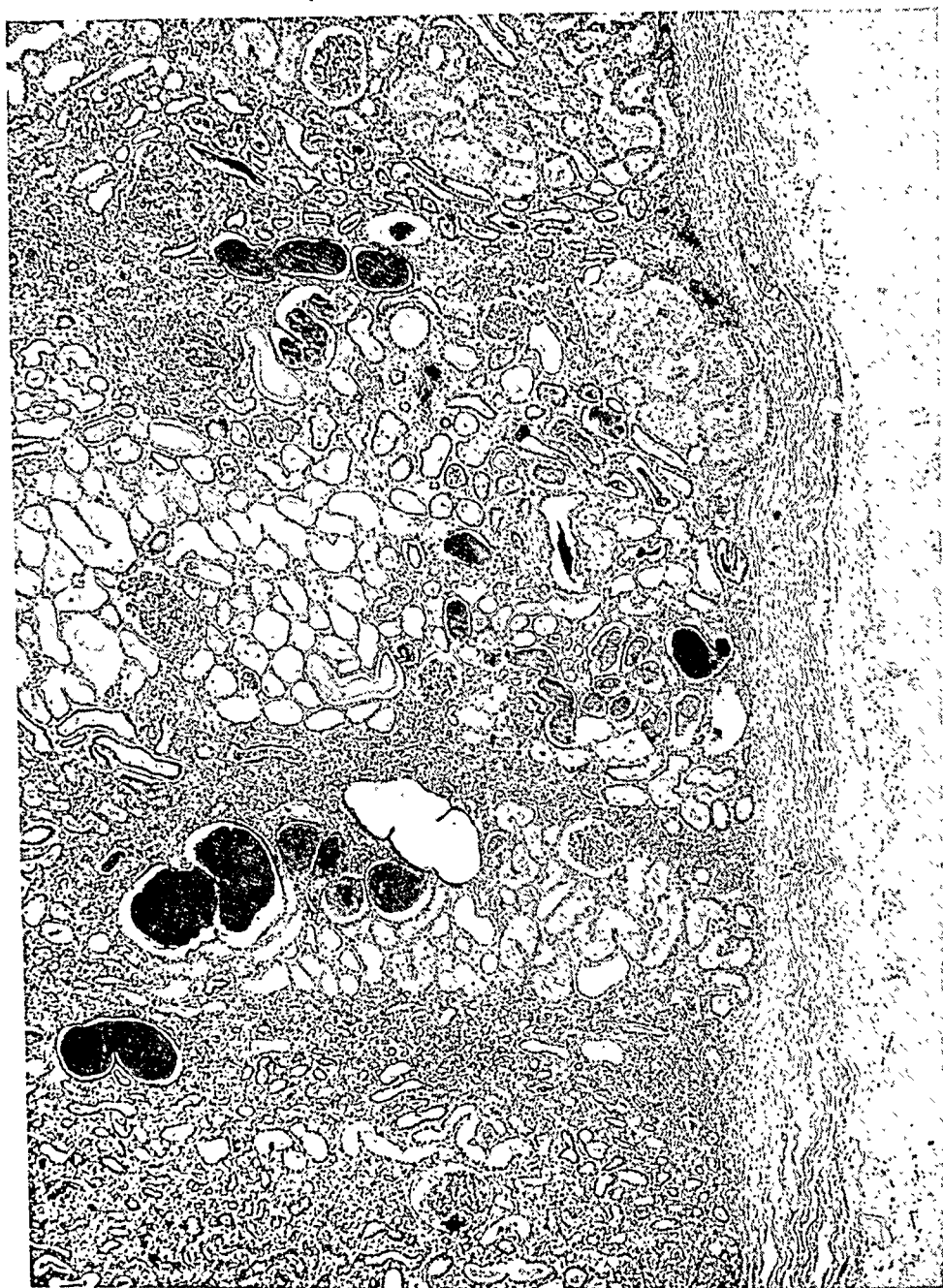


FIG. 8. Cortex of right kidney. Showing dilated tubules as contrasted with the left kidney. X 40.

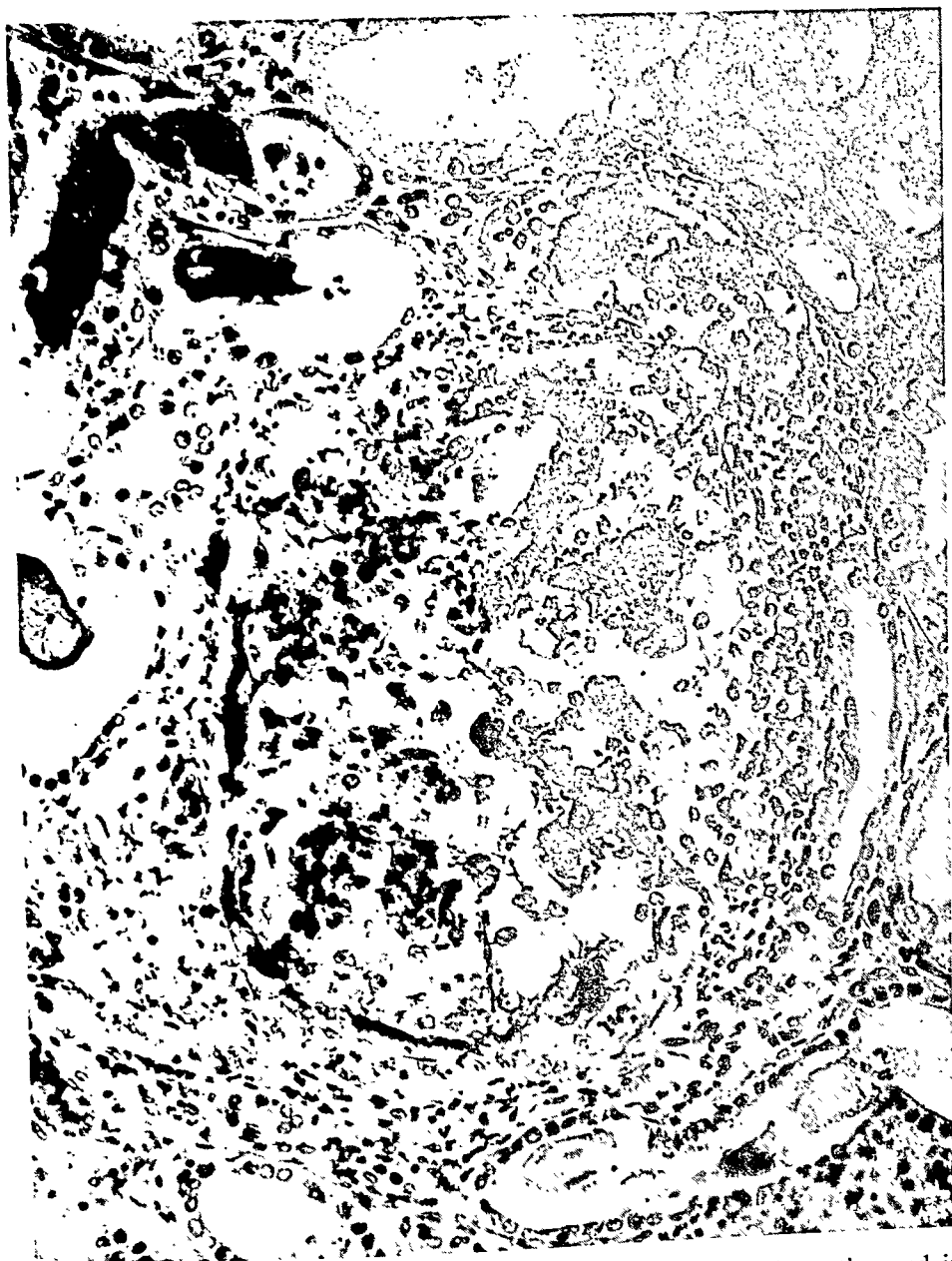


FIG. 9. Right kidney. Necrosis of glomerulus with some fibrin formation and infiltration of polymorphonuclear neutrophils in and around the glomerulus. X 250.

tion of the tuft epithelium, often associated with marked proliferation of the capsular epithelium, with fusion between the tuft and capsular epithelium. As in the first kidney, the lesion sometimes involved the whole tuft and sometimes only a portion of it. The tufts themselves showed the same changes

the majority of these tubules contained only granular material, some had hyaline casts and others red blood corpuscles in their lumens. Similar groups of dilated tubules were found deeper in the cortex but here their number was considerably smaller. Hyaline droplets in the cytoplasm of the tubu-

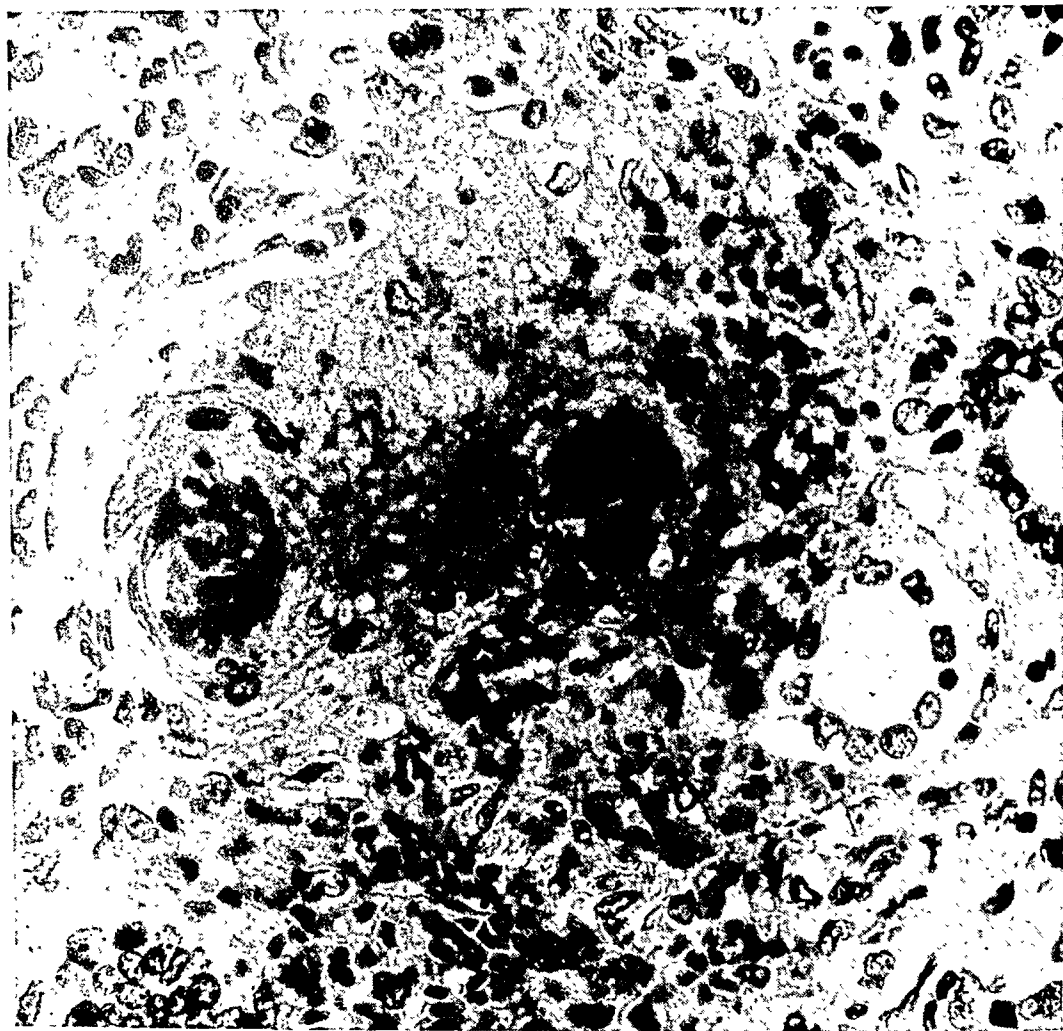


FIG. 10. Right kidney. Arteriolar hemorrhage. One vessel is cut longitudinally and can be followed into the hemorrhage. X 360.

described in the first kidney. In addition, there were some lesions of a more fulminating character. Such lesions consisted in necrosis of the arteriolar wall with necrosis and hemorrhage into the tuft and an infiltration of polymorphonuclear leukocytes, the lesion being essentially an infarct. In such glomeruli, there was associated capsular proliferation. Groups of tubules in the cortex under the capsule were dilated and their epithelium tended to be flattened. While

lar epithelium were quite common. In the sclerosed areas, the tubules were narrowed and collapsed. A few tubules contained polymorphonuclear leukocytes and in some of the collecting tubules in the pyramids there were hyaline casts and casts whose structure and staining reaction resembled hemoglobin. The blood vessel changes were essentially the same as in the other kidney: normal larger vessels, fibrous and hyaline thickening of the smaller arteries and arterioles and in

some areas a necrotizing arteriolitis. There were scattered focal hemorrhages in the pyramids. In sections stained for fat, essentially the same amount was found as in the first kidney examined, and with a similar distribution.

Adrenals: Beneath the capsule, in the

there was sclerosis. In the peri-adrenal tissue, some vessels showed lesions consisting of degeneration and hemorrhage into their walls; others contained fresh thrombi and still others were filled with organized and canalized thrombi (figure 17). There was an infiltration of lymphocytes, plasma cells,

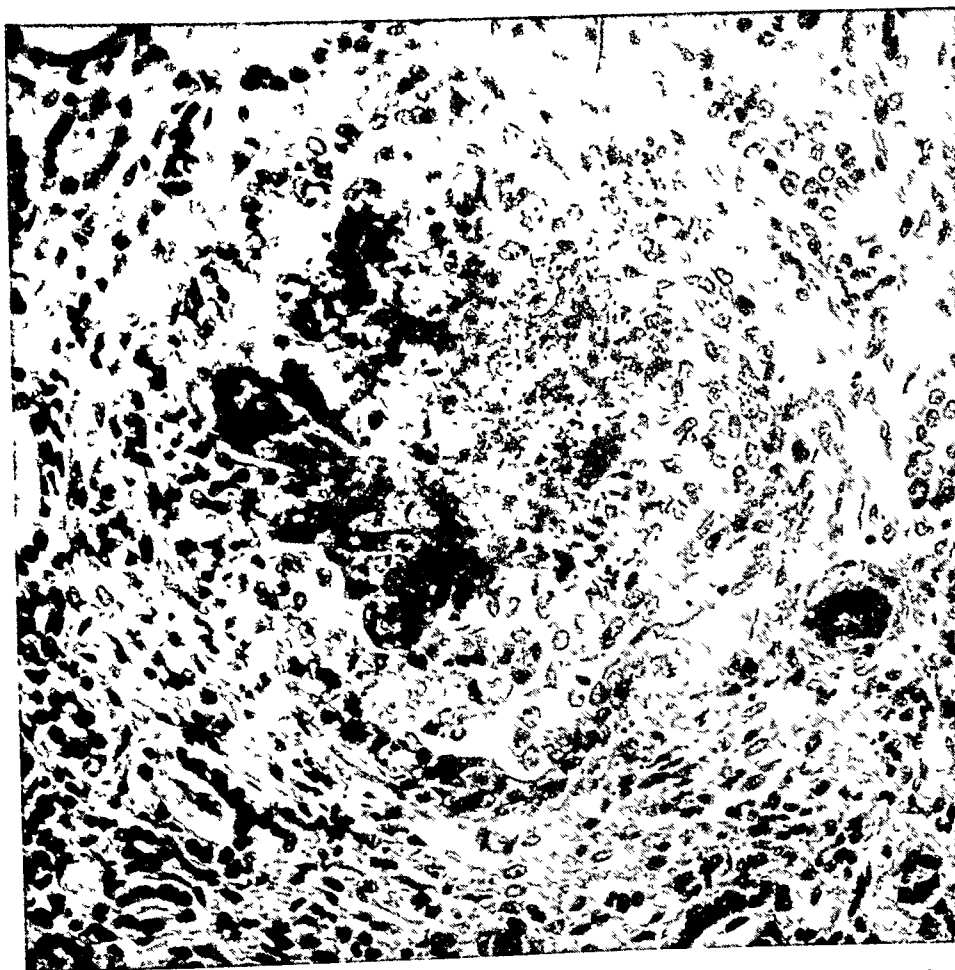


FIG. 11. Right kidney. Necrosis of glomerular tuft with hemorrhage. At the right can be seen a necrotic arteriole. X 275.

outer layers of the zona glomerulosa, there were numerous arterioles undergoing necrosis with fibrin formation in their walls. Other arterioles in this same region showed hyaline thickening of their walls. Adjacent to one necrotic arteriole (figure 16), there had been disappearance of the adrenal cells with an accumulation of large mononuclears containing fat. Scattered throughout the cortex were several focal collections of fat-laden macrophages and in one or two similar areas

and macrophages containing hemosiderin in the peri-adrenal connective tissue which appeared increased in amount. The walls of a number of thickened vessels contained a considerable amount of fat.

Aorta: There was a rare large mononuclear cell in the intima.

Bone Marrow (Vertebral): There was a normal number of cells of the erythrocytic, granulocytic and megakaryocytic series. A fair number of the last looked de-

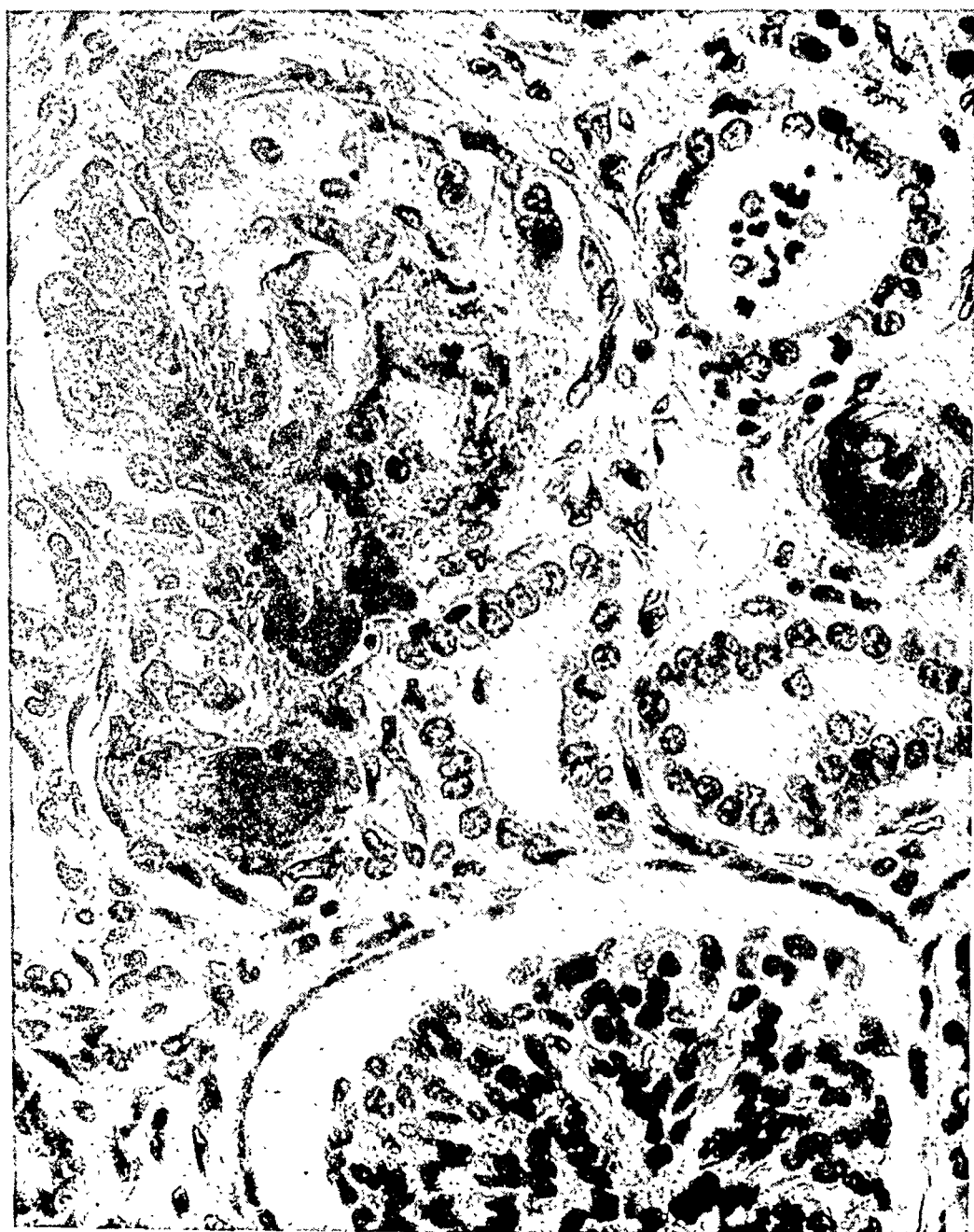


FIG. 12. Right kidney. Necrosis of arteriole and glomerulus. X 500.

generated. Focal collections of stem cells were noticeable. Plasma cells were rather numerous. Only a few arterioles could be found and they appeared normal.

Bacteriology: Cultures of the heart's blood were negative.

Quantitative and Comparative Histological Observations. We had a unique opportunity

than in the right kidney at autopsy. While the majority of the cells in the right kidney were lymphocytes, there were also numerous polymorphonuclear neutrophils, especially in foci and in the lumens of the tubules. Indeed, the number of leukocytes, many of which were necrotic, in the tubules was so great that a pyelonephritis was suspected.

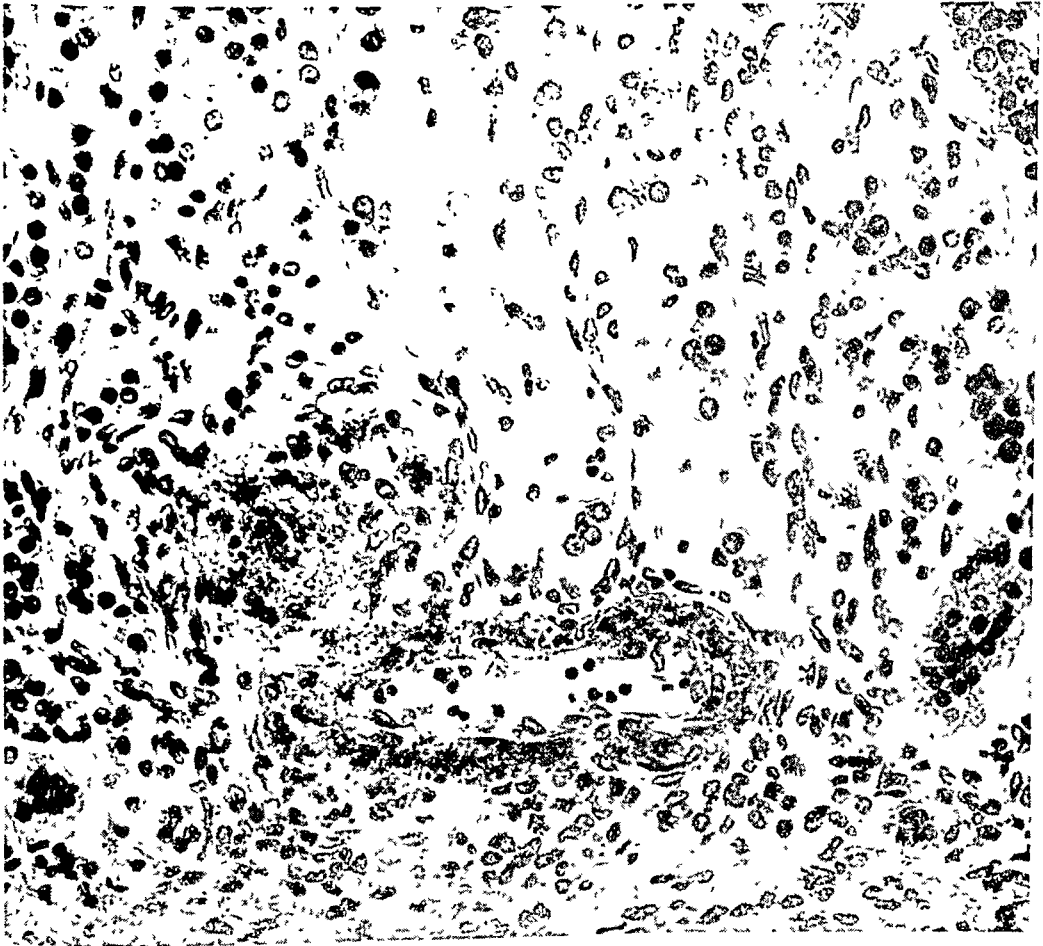


FIG. 16. Adrenal. Necrotic arteriole. Loss of parenchymatous cells below with infiltration of fat-laden macrophages. X 300.

to study the renal lesions at two different periods since one kidney was removed two months prior to the autopsy. In comparing the two kidneys, the most noticeable differences were found in the cellular infiltration of the stroma, the tubular changes, the glomerular lesions and the size of the kidneys.

The cellular infiltration in the left kidney removed surgically was much more marked

However, careful search of the sections failed to reveal any bacteria. Gross and histological study of the bladder and ureters also failed to reveal changes indicating infection.

The islands of dilated tubules found in the cortex of the autopsy specimen were noticeable and probably represented a compensatory dilatation. In this particular case there was great demand for compensatory func-

tion on the part of the remaining kidney since its load was suddenly doubled with the removal of the first kidney. The physiological studies described above demonstrate that it was able to carry on such a function during a comparatively short period.

In an effort to gain an idea of the relative

different types of lesions in the two kidneys. Obviously in both kidneys there were a number of normal glomeruli, but this number was considerably greater in the kidney removed surgically than in the kidney removed at the time of death two months later. The hypertensive type of glomerulus with thick-

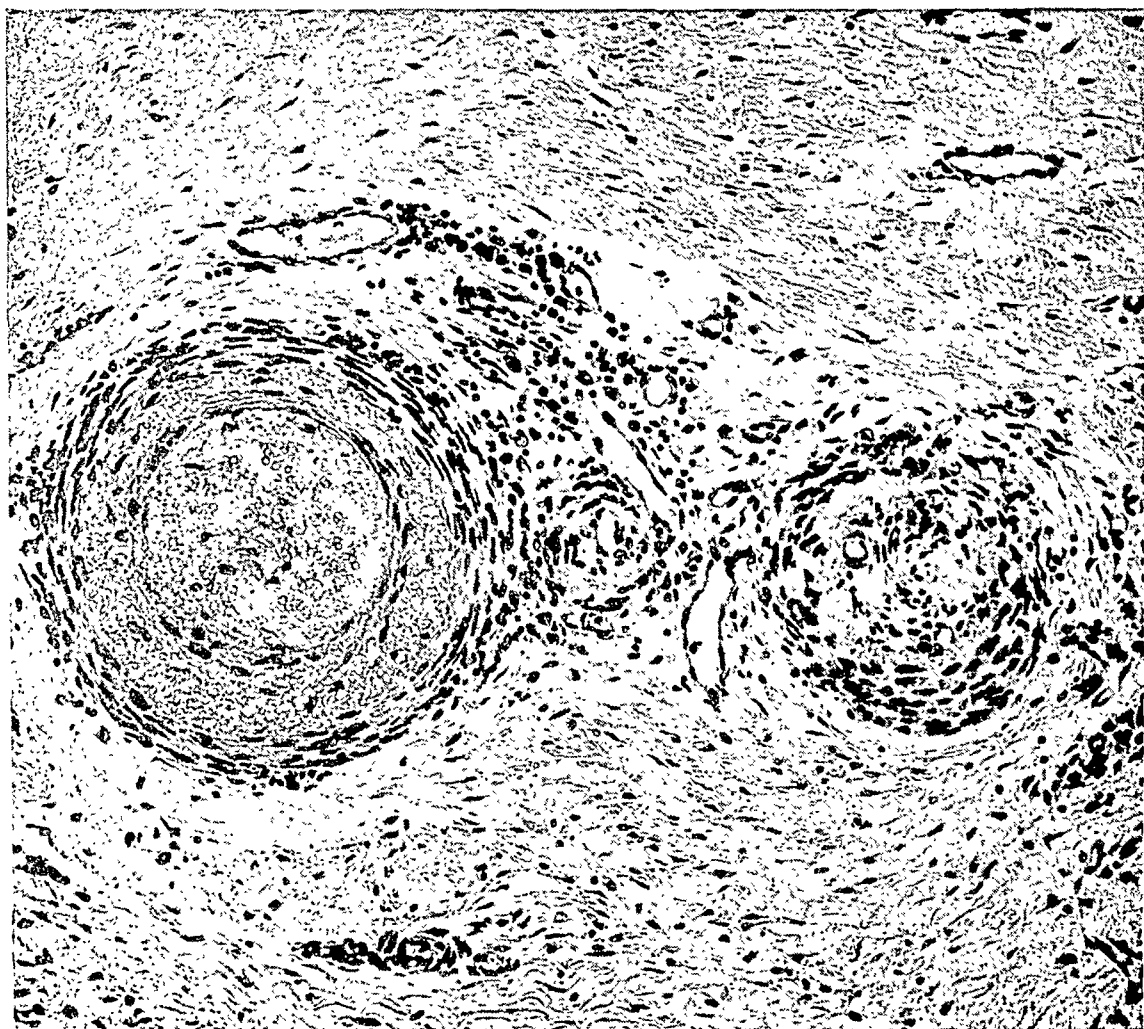


FIG. 17. Adrenal. Two arteries in periadrenal tissue. The one on the left shows hemorrhage into its wall, the one on the right contains an organized canalized thrombus. X 175.

frequency of the different types of glomerular lesions in the two kidneys, 300 glomeruli were studied in each kidney, after staining the sections with Mallory's anilin blue stain (Lee Brown modification). In this study several sections from different areas of each kidney were utilized. The results are given in table 6.

The data obtained by such a procedure serve to indicate the relative number of the

ened and wrinkled basement membrane was present in considerably larger numbers in the second kidney. Likewise hyaline, sclerotic glomeruli were more frequent in the autopsy specimen. It is of special significance that the type of glomerular lesion with an intracapillary meshwork of fibers and associated epithelial degeneration and proliferation was present in both kidneys but was somewhat less frequently found in the kidney

removed at autopsy. On the other hand, necrotizing arteriolitis and glomerular infarction were both much more prominent at the time of death.

The surgically removed (left) kidney weighed 213 gm. and was obviously considerably enlarged. The other kidney at the time of the patient's death weighed 165 gm. The size of the first was not due to operative clamping of the pedicle with resultant congestion since no evidence of this was found. It is interesting that the right kidney, in spite of its theoretical compensation, weighed almost 50 gm. less. There was no evidence

what appeared from the character of certain of the casts to be hemoglobinuria.

The acute disintegration of the glomeruli is considered a natural consequence of the thrombotic processes in vessels, with secondary acute or subacute ischemia. That under such circumstances leukocytic infiltration and other microscopic indications of an inflammatory process develop, is not unexpected. Such an abundant leukocytic infiltration was also noted by Shapiro.⁶ One may compare this histological picture in the glomeruli with the changes in the myocardium following coronary thrombosis. Infection and, partic-

TABLE VI
A COMPARISON OF THE GLOMERULAR LESIONS IN THE LEFT AND RIGHT
KIDNEYS IN THE CASE OF MALIGNANT NEPHROSCLEROSIS

	N	H	I	S
	%	%	%	%
Left kidney, Nov. 18, 1930	27	28	32	13
Right kidney, Jan. 24, 1931	12	45	23	20

N = normal glomeruli,

H = hypertensive type of glomeruli,

I = glomeruli showing lesions of glomerulonephritis with or without an associated necrosis of the afferent arterioles,

S = sclerosed glomeruli.

that this kidney was congenitally hypoplastic; therefore, presumably its weight approximated that of its mate at the time of the nephrectomy. This decrease in weight might be accounted for by the diminution in the acute inflammatory exudate and by the loss of kidney parenchyma.

The vascular hemorrhages in this case were confined to the kidneys. It is possible that some may have occurred in the brain, but unfortunately permission to examine this organ could not be obtained. Histological examination revealed that the hemorrhages in the kidney were of three types—capillary, arteriolar and intratubular. The numerous capillary hemorrhages occurred in both kidneys and were almost entirely confined to the pyramids. The arteriolar hemorrhages, on the other hand, were found in the cortex. We attach special significance to the observation that hemorrhage into the tubules was common and marked in both kidneys, and in the second kidney was associated with

ularly, the presence of bacteria in such "inflammatory reactions" is not essential. A search for local infections in the kidney in this condition, therefore, may be futile, and perhaps the wrong approach to the problem.

It was stated above that there was evidence, as judged from the clinical course and laboratory tests, of an acute exacerbation with remission and a second flare-up of the acute process in the kidneys. Interestingly enough, this was confirmed by the histological findings. In addition, a similar picture was observed also in the lungs, liver, pancreas, and adrenals. The lungs showed an organizing process, as well as recent hemorrhages. The liver showed both a healed and an acute hemorrhagic central necrosis, thus pointing to at least two acute injuries, one some time prior to the other. In both the adrenals and the pancreas, areas of sclerosis as well as active focal lesions were present. In the peri-adrenal tissue there were several vessels containing organized and re-

canalized thrombi; in addition, in the adjacent connective tissue were numerous macrophages containing hemosiderin, evidently the remains of a hemorrhagic process. One vessel in the pancreas contained an organizing thrombus (figure 15), and its wall was degenerated and filled with nuclear debris. In brief, then, there were signs of healed

steady progressive nature of the disease. However, the sudden fluctuations in the clinical course suggest periodic healing and later exacerbation of the entire process in various organs with new and diffuse involvement of areas of minute vessels, rather than the progressive spread of the vascular disease into new areas.

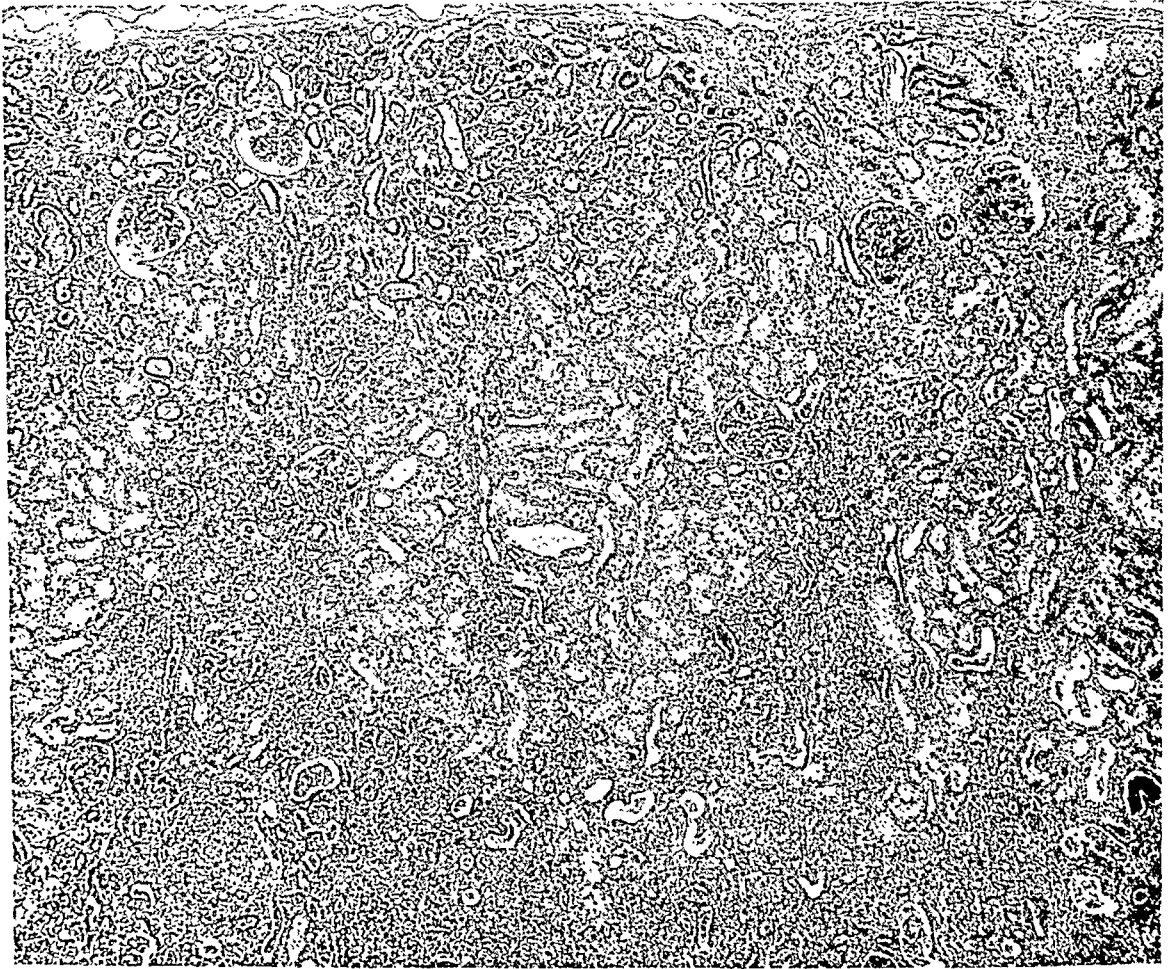


FIG. 5. Cortex of left kidney. Lack of dilated tubules. Infiltration of connective tissue with leukocytes. X 40.

lesions and acute lesions in various organs of the body indicating that there had been at least one acute attack in the past which had subsided and which was followed by another acute process found at the time of the patient's death. It is possible that with the progress of the disease more and more vascular units became involved. Thus, some minute vessels already showed chronic lesions at a time when others first became involved. Such an interpretation would indicate a

The changes noted in various organs illustrate once again that the lesions in malignant nephrosclerosis are by no means confined to the kidney but involve other organs as well. In our case, the vascular and parenchymatous involvement of the pancreas and adrenal was severe.

The acute and subacute changes in the bronchioles, atria and alveoli of the lungs with a normal state of the pulmonary blood vessels suggest that this pulmonary process



FIG 6. Left kidney. Degeneration and proliferation of epithelium of glomerulus. One mitosis in lower lefthand corner. X 250.

was not related to the specific pathology of malignant hypertension. A bronchiolitis obliterans in chronic Bright's disease has been observed recently.³² In view of the cardiac asthma and our interpretation of it, we are inclined to attribute the pulmonary changes to circulatory alterations resulting from relative and acute periodic failure of the left ventricle of the heart with secondary increased pulmonary pressure and transudations of plasma

GENERAL DISCUSSION

The occurrence of an unusually rapid blood flow through the kidney in advanced malignant hypertension aids in the interpretation of the pathogenesis of the disease. This increased flow of blood existed, notwithstanding the fact that there was present partial and complete occlusion of nu-

merous afferent arterioles and capillaries of the glomeruli. It is probable that the increased blood flow through the kidneys was maintained by the elevated systemic arterial pressure. Although the earlier experimental obser-

In our case the high arterial oxygen saturation of the blood in the renal vein together with the ruptured capillaries in the kidney indicate also that the glomerular capillary pressure was increased. The presence of dilated

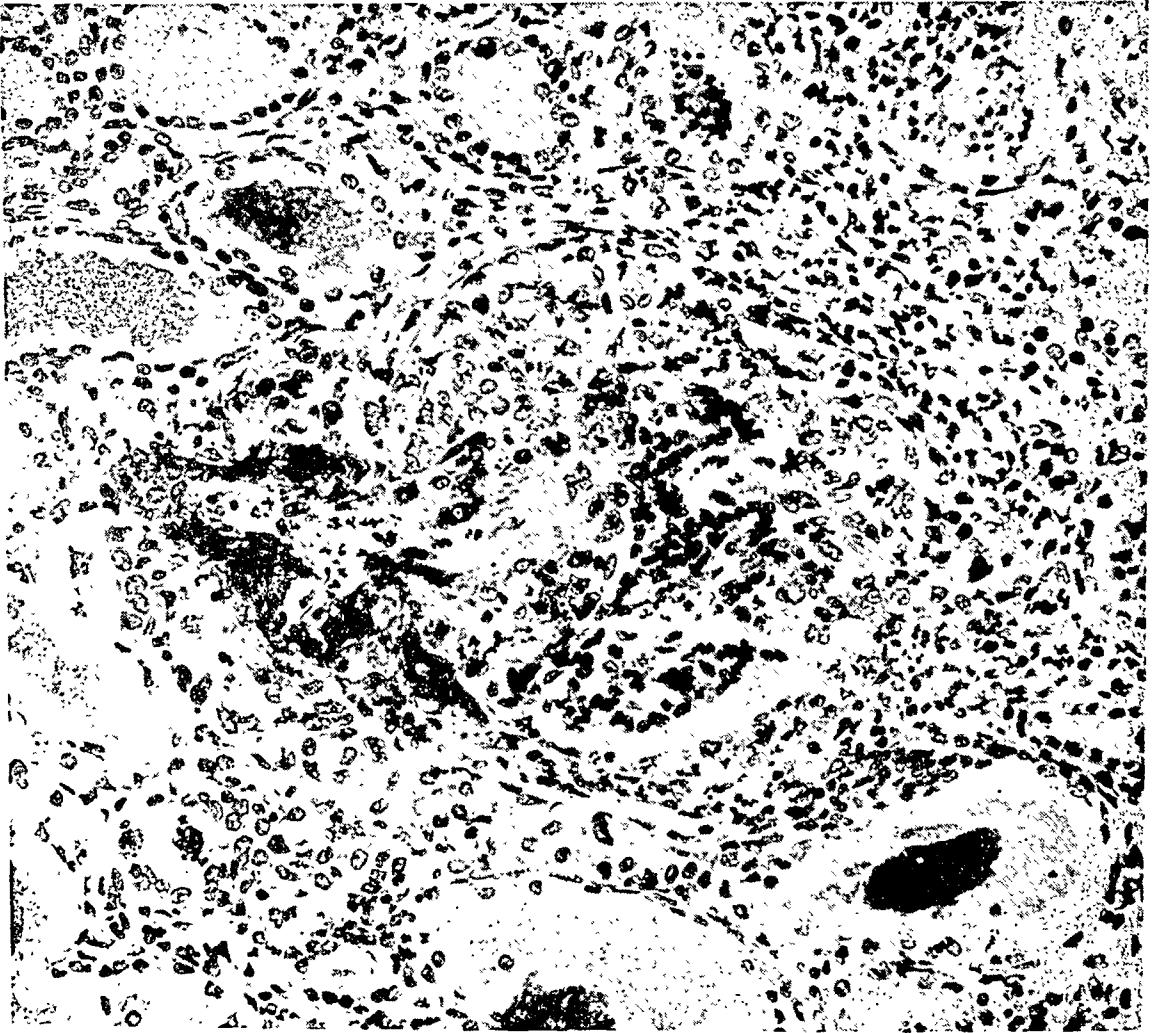


FIG. 7. Left kidney. Necrosis of arteriole and portion of glomerulus. Infiltration with polymorphonuclear neutrophils. Proliferation of glomerular epithelium. X 250.

vations of Landergren and Tigerstedt³³ suggest that blood flow through the kidney has no relation to the level of the blood pressure, the more recent studies of Ozaki³⁴ and Moritomo,³⁵ with more reliable methods, reveal that a rise in arterial pressure increases the blood flow through the kidneys in animals.

afferent arterioles and capillaries of the glomeruli, an observation made also by Shapiro,⁶ suggests an elevated pressure in the minute vessels of the glomeruli. Our finding of ruptured tubular capillaries suggests that the elevated pressure involved the tubular capillary system also, at least in a number of kidney units.

Although the histological structure and the exact distribution of the renal capillary system is not definitely established, a number of histological^{36,37,38,39} and physiological studies⁴⁰ have furnished definite evidence that the emerg-

latory mechanism makes possible an increase of the capillary pressure in the glomerulus without necessitating a change in the pressure of the tubular capillary system. Such an independent change in the pressure relations be-

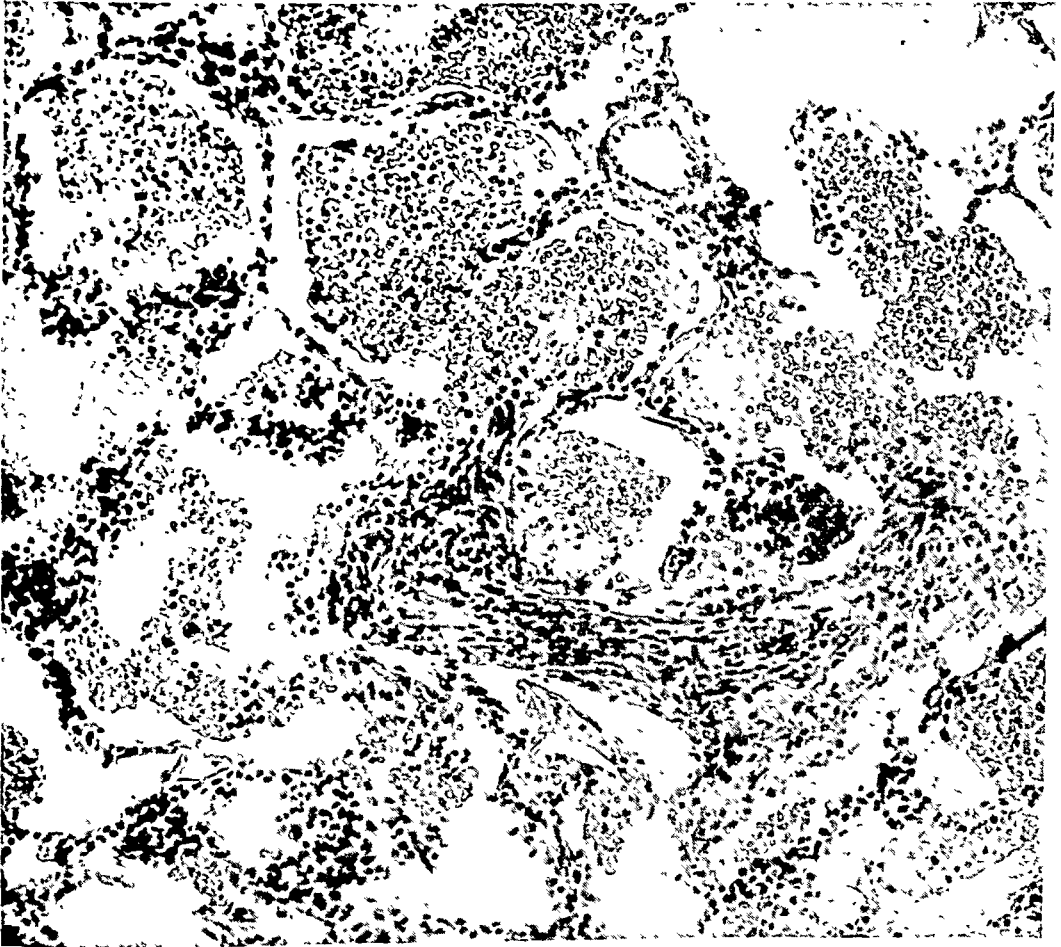


FIG. 14. Lung. One area of organized fibrin. Alveoli filled with red blood corpuscles. X 150.

ing portion of the efferent vessels of the glomeruli possesses special structures, which, probably through a sphincter-like function, allow the regulation of the blood flow through the physiological unit of the kidney. As the majority of the tubular capillaries are continuations of the glomerular capillaries,³⁹ the function of the regu-

tween the minute vessels of the glomeruli and tubules will result in better functional economy and increased filtration of urine without interference with reabsorption, so far as the latter can be influenced by hemodynamics. Depending on the degree of constriction of the efferent vessels of the glomeruli and on the simultaneous level of the

arterial blood pressure and on the size of the lumen of the afferent vessels, the glomerular capillary pressure may become elevated without a simultaneous increase or even with a decrease in the volume of blood flow through the kidney unit.

In the first place a number of the physiological units are completely eliminated. In a number of others there is a distinct structural change in the form of a thickening of the basement membrane. In these latter glomeruli, increased capillary pressure with nor-

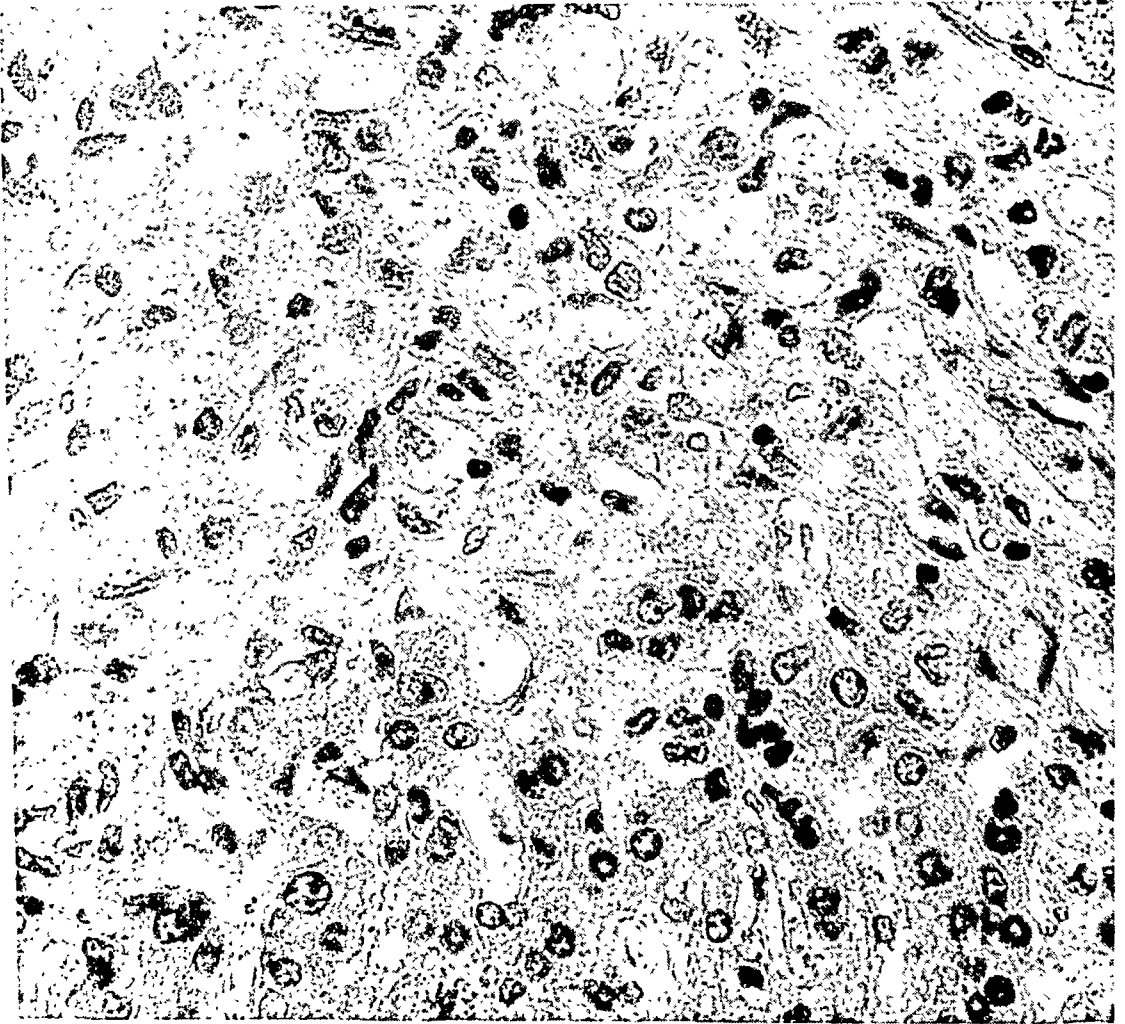


FIG. 18. Liver. Central sclerosis. X 250.

In this case of malignant nephrosclerosis, the increased blood flow together with the increased capillary pressure may be considered as a useful compensatory factor in the elimination of the waste products of the blood. In the light of the histological observations such an increased filtration pressure is beneficial for two reasons: (1)

mal or increased blood flow should improve filtration. (2) In the remaining number of normal glomeruli the circulatory changes, mainly through hypertension, induce an increased amount of filtration which compensates for the damaged glomeruli. Thus, the irregularly distributed morphological lesions of varying degree, that some-

what resemble focal glomerulonephritis, together with the observations on the functional state of the kidney suggest that in various units of the kidney the local hemodynamics as well as the secretory functions differ.

The increased volume of urine formation with fixed low specific gravity observed in the case is, therefore, not so much due to the impaired reabsorptive power of the tubules, as to the fact that in the 27 per cent of normal glomeruli, at the time the nephrectomy was performed, the volume and the velocity of the filtrate flow through the tubules was increased to a degree that prevented a correspondingly increased reabsorption by the tubules. The dilated and thin tubules in this and other cases are indications of increased filtrate flow under high intratubular pressure. In the physiological units with mild or severe lesions of the glomeruli the filtrate was probably less in volume and, therefore, as judged from the relatively normal histological appearance of the tubules, reabsorption may have occurred in a relatively more normal manner than filtration. The observation that the urea and creatinine clearance tests paralleled each other is also in harmony with this interpretation. The specific gravity, fixation of the urine volume per hour, and of the creatinine concentration index between blood and glomerular filtrate regardless of the water intake, also indicate that the kidney function was maximal in any given time. This, in view of the above findings on the hemodynamics of the kidney, is also to be expected.

Shapiro,⁶ on the basis of his observations that in malignant nephrosclerosis the afferent arterioles and capillaries of the glomeruli were dilated, and that in-

jected India ink entered the wide afferent vessels of the glomeruli with ease, although the resistance of the kidney vessels was considerably increased, concluded that the pathogenesis of kidney changes depends "not on glomerular ischemia or on arteriolar occlusion, but on a hyperemia associated with a retardation of flow". This retardation is explained by him in accordance with Ricker's theory of a neurogenic dissociation in reaction between arterial constriction and peripheral dilatation. Shapiro does not offer any histological or other evidence, however, "for this neurogenic dissociation" nor for the existence of outstanding constriction of the larger or smaller arteries. His explanation would also fail to offer any rational explanation for the presence simultaneously of dilated and normal caliber individual glomerular capillary loops within the same glomerulus and hence supplied by the same small artery. The explanation offered by him would also necessitate the inference that the capillary pressure is decreased or at least not particularly increased in the glomeruli, a concept which is difficult to harmonize with frequent rupture of the kidney capillaries in this condition.

We realize that the evidence available from Shapiro's observations and the studies presented here do not permit at present the formation of a concept supported by sufficiently detailed direct observations; nevertheless, we favor the following working *hypothesis*, which in our opinion harmonizes all of the observations so far made.

The state of affairs in different units of the kidney in malignant nephrosclerosis at a given time differs considera-

bly. In the early stage of the disease a moderate constriction occurs in a certain number of efferent vessels of the glomeruli. These portions of the kidney capillary system have a rather specific structure, and the rôle of this vascular portion is similar in the kidney to that of the arterioles of other vascular areas. Their constricted state would correspond to the constricted arterioles in other organs observed in malignant hypertension. In accordance with the histological nature of malignant nephrosclerosis the degree of constriction is irregularly distributed. This focal scattered distribution of the histological lesions which was emphasized in this case has also been observed by us in a number of other cases. In the kidney units with severe vascular constriction which is out of proportion to the height of the arterial blood pressures relative stasis with increased pressure in the minute vessels, for reasons discussed above, will lead to dilatation of the vessels central to the emerging efferent portion of the glomerular vessel. It is this absolute or relative stasis with increased pressure in the glomerular vessels that leads to imbibition of metabolites by the adjacent structures, with resulting changes in the basement membrane as well as in the vessel wall itself. Simultaneously with these marked changes, in some of the glomeruli, with the progressively increasing arterial hypertension, the above described compensatory changes with rapid local blood flow and increased glomerular filtration occur. As the pathological process advances, involving larger numbers of vascular units, the number of normal units becomes so few that effective compensatory

elimination cannot be maintained and uremia ensues. Thus, near to the time of death there may be perhaps a decrease in the total blood flow through the kidney, while earlier the total blood flow, as was the case in this patient, is considerably increased. But even if the total blood flow is less than normal near to death, the volume flow through the remaining individual normal units must be increased considerably. This concept is in harmony with the general character of the circulation in arterial hypertension⁴¹ and satisfactorily accounts for all the abnormalities detected in malignant hypertension.

It is obvious that the mechanisms of benign and malignant nephrosclerosis show a certain degree of similarity. There are, however, a number of differences in the clinical course and in the histology of the kidney in the two conditions. The youthful age of the patients, the fulminating fatal course, the markedly irregular distribution of the vascular lesions, and the character of the eyegrounds all suggest essential differences.

It is rather unfortunate that, because of the similarity in the mechanism of the two conditions, often no distinction in the etiology is made. The etiology of malignant hypertension is unknown. From the history and clinical study of a number of cases of malignant hypertension, we have been impressed with the frequency of severe infections. Tonsillar and peritonsillar abscesses, severe follicular tonsillitis, rheumatic fever, perinephritic abscess, pyelitis, and pyelonephritis were found in the cases observed by us in the past. Since it has been observed that the infection had often subsided at the time

when symptoms of malignant hypertension developed, one may justifiably assume that in malignant arterial hypertension an acute tissue response exists, which has a relation to infection, but which, if once precipitated, proceeds independently of infection. This indirect relationship between infection and malignant hypertension is apparently similar to the relation that exists between infection and certain allergic states.

SUMMARY

1. A study of malignant arterial hypertension with malignant nephrosclerosis is reported from observations on a case in which left nephrectomy was performed because of unilateral bleeding and suspected malignancy. The clinical course of the disease and the hemodynamics, function, and histological structures of the kidneys are analyzed and correlated.

2. Observations on the hemodynamics of the kidneys in three cases with normal kidney functions and cardiovascular systems, in which surgical suspension of the kidneys under spinal anesthesia was performed, served as controls.

3. The oxygen difference between the arterial blood and the blood from the renal vein in the three control subjects varied between 1.3 and 3.0 vol. per cent with an average of 2.4 vol. per cent. The average amount of oxygen taken from the blood by the kidney was 13 per cent of the average oxygen content of the arterial blood.

4. A comparison of the arteriovenous oxygen difference in the kidneys in these three subjects with that in the brain, heart, arm and leg indicates a

low oxygen difference and a relatively rapid blood flow through the kidneys.

5. No oxygen difference existed between the arterial blood and the blood from the renal vein of the patient with nephrosclerosis, which is interpreted as an indication of unusually rapid flow through the kidney.

6. The urea nitrogen changed from 13.0 mg. to 10.0 mg. per 100 c.c. in renal artery and vein in one of the control subjects and from 36.1 mg. to 32.5 mg. in the patient with nephrosclerosis. The urea and creatinine clearance performed during the surgical operation indicated adequate kidney function. The concentrations of creatinine and chlorides in the renal arterial and in the renal venous blood samples showed no demonstrable differences either in the control case or in the case with nephrosclerosis.

7. The nature of the functional disturbance of the right kidney after left nephrectomy was studied with repeated and simultaneously performed urea and creatinine clearance tests, and with the concentration and dilution tests.

8. The structures of the glomeruli of the left kidney were quantitatively compared with those of the right kidney; and it was demonstrated that within 67 days the number of glomeruli with thickened basement membrane and complete sclerosis increased considerably. The vascular sclerosis also became more extensive during this period.

9. Appearance of blood in the urine was caused by rupture of the minute blood vessels of the glomeruli and tubules as a result of increased pressure. The source of blood in the urine in ma-

lignant nephrosclerosis may be unilateral.

10. It has been demonstrated again that malignant hypertension is a diffuse disease of the vascular system with characteristic lesions in a number of organs.

11. The clinical course of the disease, the function of the kidney, and the histological analysis of the minute blood vessels of the kidneys and other

organs in this case of malignant hypertension indicated a tendency to fluctuate between improvement and relapses.

12. A concept is presented which correlates and interprets functional and structural changes observed in malignant nephrosclerosis with arterial hypertension.

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BIBLIOGRAPHY

- ¹VOLHARD, F., and FAHR, K. T.: Die Brightsche Nierenkrankheit; Klinik. Pathologie und Atlas, 1914, Julius Springer, Berlin.
- ²LÖHLEIN, M.: Zur Pathogenese der vasculären Schrumpfniere, *Med. Klin.*, 1916, xii, 741, 872, and 1042.—Über Schrumpfnieren, *Beitr. z. path. Anat. u. z. allg. Path.*, 1919, lxiii, 570-632.
- ³FAHR, T.: Über atypische Befunde aus den Kapiteln des Morbus Brightii nebst anhangweisen Bemerkungen zur Hypertoniefrage, *Virchow's Arch. f. path. Anat.*, 1924, ccxlviii, 323-336.
- HENKE, F., and LUBARSCH, O.: *Handbuch der speziellen pathologischen Anatomie u. Histologie*, Vol. 6, 1925, Julius Springer, Berlin.
- ⁴JORES, L.: Warum schreiben wir der Sklerose der Nierenarteriolen ein Bedeutung für das Zustandekommen gewisser Formen von Schrumpfnieren zu?, *Virchow's Arch. f. path. Anat.*, 1917, ccxxiii, 233-242.
- ⁵BELL, E. T., and CLAWSON, B. J.: Primary (essential) hypertension; study of 420 cases, *Arch. Path.*, 1928, v, 939-1002.
- ⁶SHAPIRO, P. F.: Malignant nephrosclerosis, pathogenesis, *Arch. Int. Med.*, 1931, xlviii, 199-233.
- ⁷STERN, M.: Über einen besonders akut verlaufenen Fall von Arteriolonekrose der Nieren mit dem makroskopischen Bilde der "grossen bunten Niere", *Virchow's Arch. f. path. Anat.*, 1924, ccli, 718-731.
- ⁸FISHBERG, A. M.: Anatomic findings in essential hypertension, *Arch. Int. Med.*, 1925, xxxv, 650-668.—The arteriolar lesions of glomerulonephritis, *ibid.*, 1927, xl, 80-97.
- ⁹MURPHY, F. D., and GRILL, J.: So-called malignant hypertension: a clinical and morphological study, *Arch. Int. Med.*, 1930, xlvi, 75-104.
- ¹⁰VOLHARD, F.: Der arterielle Hochdruck, *Verhandl. d. deutsch. Gesellsch. f. innere Med.*, 1923, xxxv, 134-184.
- ¹¹KLEMPERER, P., and OTANI, S.: "Malignant nephrosclerosis" (Fahr), *Arch. Path.*, 1931, xi, 60-117.
- ¹²MEYER-STETTIN, O.: Über das Vorkommen und die Bedeutung entzündlicher Gefässveränderungen in den Nieren mit besonderer Berücksichtigung der Glomerulitis, der sekundären und genuinen Schrumpfnieren, *Verhandl. d. deutsch. path. Gesellsch.*, 1923, xix, 352-361.
- ¹³STERNBERG, B.: Thrombo-angioneurotic changes of the kidneys in chronic nephritis, *Arch. Int. Med.*, 1929, xlv, 272-280.
- ¹⁴ASK-UPMARK, E.: Über juvenile maligne Nephrosklerose und ihr Verhältnis zu Störungen in der Nierenentwicklung, *Acta path. et microbiol. Scandinav.*, 1929, vi, 383-442.
- ¹⁵WEISS, S., and ROBB, G. P.: The mechanism and treatment of the paroxysmal dyspnea and asthma associated with heart disease, *New Eng. Jr. Med.*, 1931, ccv, 1172.—The treatment of cardiac asthma (paroxysmal cardiac dyspnea), *Med. Clin. N. Am.*, 1933, xvi, 961-971.

- ¹⁶TANGL, F.: Calorimetrie der Nierenarbeit, *Biochem. Ztschr.*, 1913, liii, 36-40.
- ¹⁷RHOADS, C. P., VAN SLYKE, D. D., HIL-
LER, A., and ALVING, A.: Studies of
renal metabolism, *Proc. Soc. Exper.
Biol. and Med.*, 1931, xxviii, 776.
- ¹⁸WEISS, S., and LENNOX, W. G.: Cerebral
circulation; cerebral blood flow and the
vasomotor response of the minute ves-
sels of the human brain to histamine,
Arch. Neurol. and Psychiat., 1931, xxvi,
737-744.
- ¹⁹WEISS, S., and ELLIS, L. B.: Unpublished
observations.
- ²⁰KLEIN, O.: Zur Bestimmung des zirkula-
torischen Minutenvolumens beim Men-
schen nach dem Fickschen Prinzip (Ge-
winnung des gemischten venösen Blutes
mittels Herzsondierung), *Münch. med.
Wchnschr.*, 1930, lxxvii, 1311-1312.
- ²¹CSERNA, S., and KELEMEN, G.: Grösse der
Arbeit kranker Nieren. Experimentelle
Untersuchungen, *Biochem. Ztschr.*, 1913,
liii, 41-68.
- ²²SHEEHAN, H. L.: The renal circulation
rate in the rabbit, *Jr. Physiol.*, 1932,
lxxiv, 214-220.
- ²³DUNN, J. S., KAY, W. W., and SHEEHAN,
H. L.: Elimination of urea by mam-
malian kidney, *Jr. Physiol.*, 1931, lxxiii,
371-381.
- ²⁴PICARD, J.: De la présence de l'urée dans
le sang et de sa diffusion dans l'organ-
isme à l'état physiologique et à l'état
pathologique, Thèse, 1856, Strassbourg.
- ²⁵MÖLLER, E., MCINTOSH, J. F., and VAN
SLYKE, D. D.: Studies of urea excre-
tion; relationship between urine volume
and the rate of urea excretion by nor-
mal adults, *Jr. Clin. Invest.*, 1928, vi,
427-465.
- ²⁶REHBERG, P. B.: Studies of kidney func-
tion. I. The rate of filtration and re-
absorption in the human kidney, *Bio-
chem. Jr.*, 1926, xx, 447-460.
- ²⁷ELLIS, L. B., and WEISS, S.: Normal vari-
ations in results of renal function tests,
with a discussion of their physiological
significance, *Am. Jr. Med. Sci.* (in press).
- ²⁸MALLORY, F. B.: The principles of path-
ologic histology, 1914, W. B. Saunders,
Philadelphia.
- ²⁹MCGREGOR, L.: The finer histology of the
normal glomerulus, *Am. Jr. Path.*, 1929,
v, 545-558.
- ³⁰MCGREGOR, L.: The cytological changes
occurring in the glomerulus of clinical
glomerulonephritis, *Am. Jr. Path.*, 1929,
v, 559-586.
- ³¹MCGREGOR, L.: Histological changes in the
renal glomerulus in essential (primary)
hypertension; study of 51 cases, *Am. Jr.
Path.*, 1930, vi, 347-366.
- ³²EHRRICH, W., and MCINTOSH, J. F.: Path-
ogenesis of bronchiolitis obliterans; ob-
servations in cases of Bright's disease,
Arch. Path., 1932, xiii, 69-79.
- ³³LANDERGREN, E., and TIGERSTEDT, R.: Stu-
dien über die Blutvertheilung im Körper.
Zweite Abhandlung: Die Blutzufuhr zu
der Niere, *Skandin. Arch. f. Physiol.*,
1892, iv, 241-280.
- ³⁴OZAKI, M.: Pharmakologie der Nieren-
gefässe, *Arch. f. exper. Path. u. Phar-
makol.*, 1927, cxxiii, 305-330.
- ³⁵MORITOMO, M.: Über die durch die Niere
fliessende Blutmenge und ihre Abhäng-
igkeit von Blutdruck, *Arch. f. d. ges.
Physiol.*, 1928, ccxxi, 155.
- ³⁶KÖLLIKER: Handbuch der Gewebelehre des
Menschen, 1852, W. Engelmann, Leipzig.
- ³⁷RENAUT, J. L.: *Traité d'histologie pra-
tique*, 2 vols., 1889-1899, Lecrosnier et
Babé, Paris.
- ³⁸BENSLEY, R. D.: The efferent vessels of
the renal glomeruli of mammals as a
mechanism for the control of glomerular
activity and pressure, *Am. Jr. Anat.*,
1929, xlv, 141-169.
- ³⁹AUGIER, M.: Circulation capillaire arté-
rielle rénale et son importance physiolo-
gique chez l'homme, *Ann. d'anat. path.*,
1930, vii, 897-900.
- ⁴⁰RICHARDS, A. N., and SCHMIDT, C. F.: A
description of the glomerular circulation
in the frog's kidney and observations
concerning the action of adrenalin and
various other substances upon it, *Am. Jr.
Physiol.*, 1924, lxxi, 178-208.
- ⁴¹WEISS, S., and ELLIS, L. B.: The quan-
titative aspects and dynamics of the
circulatory mechanism in arterial hyper-
tension, *Am. Heart Jr.*, 1930, v, 448-468.

Changes Observed in the Heart Shadow in Toxic Goiter before and after Treatment*†

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THE object of this study was to determine what changes take place in the size and shape of the heart before and after subtotal thyroidectomy for hyperthyroidism. One hundred and fifteen cases were observed in which roentgenograms were taken before and at various phases during and after treatment.

CLINICAL MATERIAL:

ROENTGENOGRAPHIC METHOD

The group of patients studied in this report do not represent a consecutive series. Forty-six cases were followed from a consecutive series of one hundred¹; the remainder were isolated cases which we have collected during the past five years. Roentgenograms were taken when the patient was first seen at the Clinic or within twenty-four hours after admission to the hospital. There were a few cases in which this was felt to be unwise owing to the patient's critical condition. The delay in such cases was rarely longer than two or three days. In seven cases, roentgenograms were taken again be-

fore operation and in the remainder, observations were made from one month to two years after operation, the majority within one year. Fluoroscopic observations were made in many of these patients, but orthodiagraphic tracings were not made.

Exposures were made with the subject standing at a seven-foot distance, during quiet breathing. The length of exposure time varied somewhat in the different hospitals but this could not account for the large differences in size found in some cases, nor for the changes found when all roentgenograms were made by the same person and with the same machine.

Measurements were made in the usual way and were then rechecked when all the films on each subject were available for comparison. This made possible a more uniform method of placing the points from which measurements were taken. When fluid was present in the chest, measurements were either impossible or less accurate than in the usual film. For this and other reasons, measurements alone cannot always be used to draw conclusions as to the change in the size of the heart shadow.

Comparisons of films were made in the following way: The contour of the

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heart, great vessels, diaphragm, and lateral chest wall were outlined (on all but nine films). The transverse processes at the root of the first rib and the first rib on the two films were superimposed and the lateral chest walls were made to coincide as nearly as possible. The outline of the heart on the underlying film could thus be seen plainly through the superimposed film, upon which it was then traced. Thus, on one film the outlines of both films were registered and the difference in the transverse diameter of the chest, the height of the diaphragm, and the changes in size and position of the heart could more clearly be seen and compared.

Even by this method of comparison and measurement, the statement that the heart shadow has changed in size is in many cases a statement of opinion and not of fact.

For instance, while a lower diaphragm and a relatively larger heart shadow in a follow-up plate mean an absolute increase in the size of the cardiac shadow, a lower diaphragm and a smaller heart shadow may or may not indicate a decrease in size. Thus all factors must be considered in each case.

AVERAGE HEART MEASUREMENTS BEFORE AND AFTER OPERATION

We obtained 46 roentgenograms after operation from a series of 100 consecutive cases of toxic goiter that had been roentgen-rayed before operation. The transverse diameters of the heart and the transverse diameters of the chest were averaged in these cases. In this group the transverse diameters of the heart after operation were larger

in 19 cases and smaller in 23 cases and the same in four cases.

The average transverse chest diameter before operation was 23.97 centimeters and after operation 24.56 centimeters. The transverse heart diameters averaged 13.07 centimeters before operation and 13.18 centimeters after operation. These averages would tend to indicate that the transverse diameters remain essentially unchanged and that the transverse diameters of the chest were increased by .6 centimeter. Such averages are misleading in considering individual cases, yet indicate the general trend that very little change takes place in the group as a whole. It would be possible, of course, for a true decrease in size of some cases to be offset by an apparent increase due to higher diaphragms in others, with a consequent maintenance of the same average transverse heart diameters for the group. Where this occurred the average transverse measurement of the heart would remain the same, though the average heart size was actually decreased. Our data could not safely be interpreted in this way.

From superimposed films it was concluded that the heart shadows of two of this series of 46 cases were larger, five questionably larger, and five smaller. Most of the cases with smaller shadows postoperatively in this series of 46 unselected patients had been admitted with congestive heart failure and auricular fibrillation.

A study of all the cases showing larger heart shadows after operation revealed that the majority had hypertension, coronary disease, rheumatic heart disease, persistent auricular fibrillation, or borderline myxedema. Large

gains in weight might reasonably be expected to be followed by larger heart shadows. Actually this was not conclusively demonstrated, although the evidence was quite suggestive in several cases.

INFLUENCE OF RHYTHM AND OF CONGESTIVE FAILURE IN CHANGES IN CARDIAC MEASUREMENTS

Normal Heart Rhythm without Congestive Heart Failure. Roentgenograms were taken on admission to the hospital and no sooner than two months later after operation in 80 cases of hyperthyroidism with normal rhythm. Twenty-three of these showed apparent changes in the heart shadow in the second plate as follows: In nine instances the heart was definitely larger and in six more questionably larger; in only six cases was the heart shadow definitely smaller; in two others the decrease in size was questionable.

Normal Heart Rhythm with Congestive Heart Failure. Seven cases showed congestive heart failure and normal rhythm. In one, the heart shadow was questionably larger when the patient was symptom-free, in two there was no definite change, and in four the heart shadows were probably smaller after clearance of heart failure. Three of these latter showed pleural fluid so that the measurements were only approximate, but comparison of the films showed obvious reduction in size. All of these cases showed coincident cardiovascular disease.

Auricular Fibrillation without Congestive Heart Failure. All of the observed patients who had auricular fibrillation without congestive heart failure on admission to the hospital, and

subsequently resumed normal rhythm, were operated upon before the normal rhythm returned. Consequently, we have no evidence as to the effect on the heart shadow when the transition from auricular fibrillation to normal rhythm occurs before relief of thyroid toxicity. We have taken roentgenograms before, during, and after postoperative auricular fibrillation. The results suggest an increase in size of the auricles from this irregularity alone. We observed an increase in size of the heart shadow following the onset of auricular fibrillation in a patient with exophthalmic goiter, mitral stenosis, and normal rhythm, who developed an attack of acute recurrent rheumatism a few days after hemithyroidectomy. Parkinson and Cookson² have recently described several cases showing an increase in the size of the heart shadow after the onset of auricular fibrillation.

Of eight cases in this series with auricular fibrillation uncomplicated by congestive heart failure, three showed postoperatively a definite reduction in the size of the heart shadow after normal rhythm was restored. Decrease in size was possibly present in the five others because of smaller transverse heart measurements, but the higher position of the diaphragms in these cases made the interpretation doubtful. Because there was so little difference in the superimposed films, the evidence did not appear sufficient to warrant a definite statement. One case with persistent auricular fibrillation appeared to show a larger shadow in the second film.

Auricular Fibrillation with Congestive Heart Failure. There were 16 cases with auricular fibrillation and conges-

tive heart failure and one with auricular flutter and congestive heart failure. Of these, 13 showed normal rhythm when the roentgen-rays

larger shadow. The latter case had hypertension and coronary disease and had had a mild recurrence of congestive heart failure although normal



FIG. 1 A. Heart shadow in a young woman, aged 31, with exophthalmic goiter, auricular fibrillation, and slight congestive heart failure. B.M.R. + 101, pulse 98, weight 108, blood pressure 160/90. Note prominence of pulmonary arc as well as region of left auricle.

were repeated. Of these 13 cases, nine showed definitely smaller heart shadows (see figure 1), two showed questionably smaller heart shadows, one showed no change, and one showed a

rhythm was present. The questionable cases probably were smaller as shown by the superimposed shadows, but the presence of fluid in the chest rendered the conclusions untrustworthy.

Four of the cases with auricular fibrillation and congestive heart failure did not have a return of normal rhythm after operation. Of these, two were

Thus it seems probable that auricular fibrillation is attended by some dilatation of the auricles and, in some instances, by dilatation of the ventri-

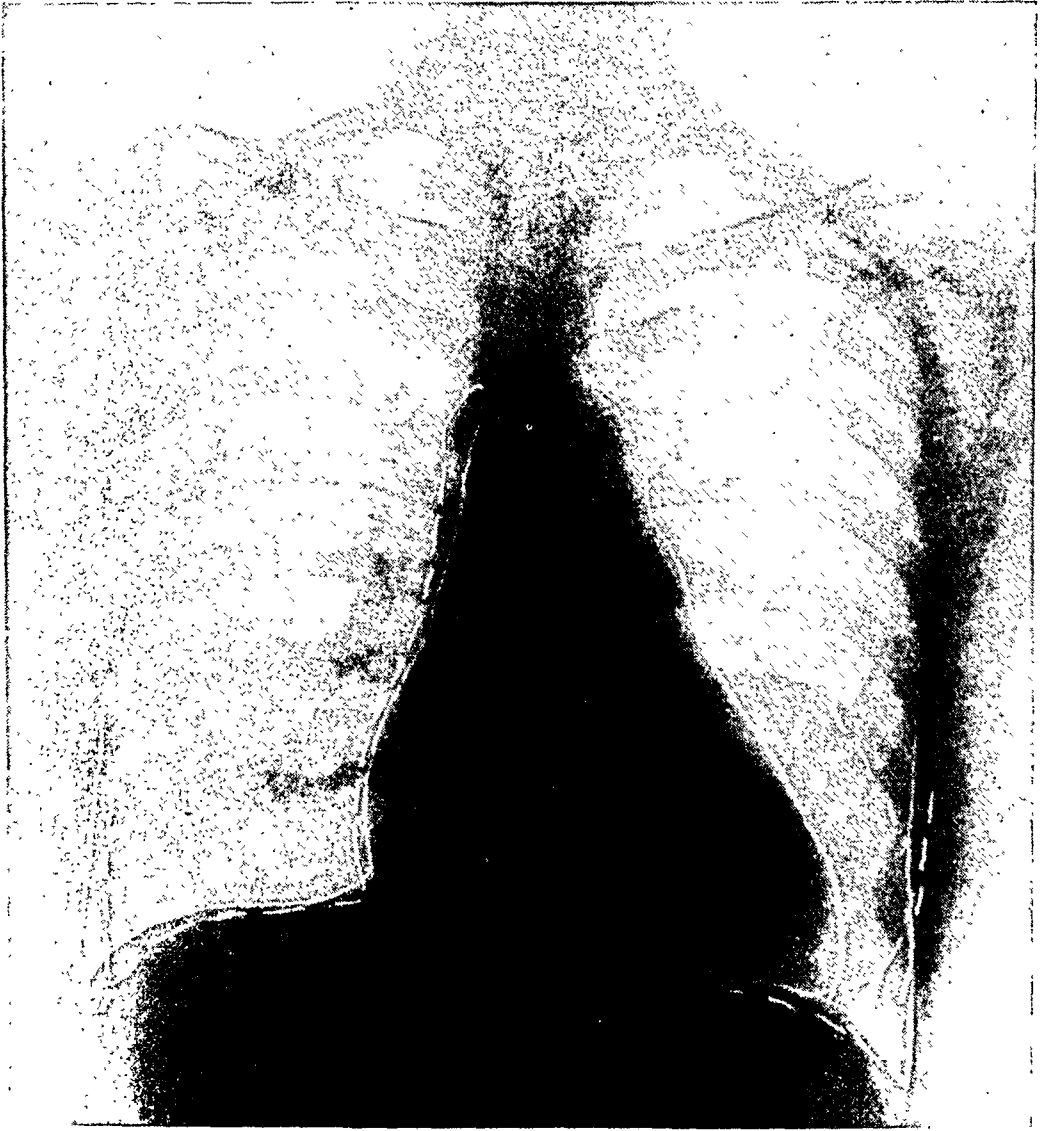


FIG. 1 B. Heart shadow 12 months later. Normal rhythm present. B.M.R. + 11, pulse 84, weight 120, blood pressure 140/90. Still slightly toxic and on Lugol's solution. The outlines of each film is superimposed upon the other. Note marked reduction along left side with diaphragms at same level. The prominence of the pulmonary arc persists.

questionably larger, one questionably smaller, and one definitely smaller.

In table 1 are shown the average measurements before and after treatment in this group of cases. It is to be noted that all measurements are smaller except the chest diameter.

cles. While we have made a sharp clinical distinction between patients with congestive heart failure and those without congestive heart failure, it is obvious, of course, that such a sharp differentiation cannot be made in all cases. Certainly, various degrees of

TABLE I
AVERAGE MEASUREMENTS BEFORE AND AFTER TREATMENT IN 16 CASES WITH AURICULAR
FIBRILLATION AND CONGESTIVE HEART FAILURE

	Average transverse diameter of chest in cms.	Average length in centi- meters	Average left border in centi- meters	Average right border in centi- meters	Average base in centi- meters	Average great vessels in centi- meters
Before treatment	23.8	16.1	10.6	5.1	10.6	8.1
After treatment	24.3	15.3	9.8	4.6	9.9	7.2

decompensation may be present before clinical signs of edema are manifest. When clear-cut congestive heart failure was present with auricular fibrillation, the heart shadow was larger than later when the fibrillating heart became well compensated. Further reduction seems to have taken place when normal rhythm was restored (figure 2).

CHANGES OBSERVED BEFORE OPERATION IN CASES WITH CONGESTIVE HEART FAILURE

Seven cases with congestive heart failure had roentgen-rays taken on admission and again after clearance of congestive heart failure. Five of these had auricular fibrillation and two had normal rhythm. Reduction in the size of the heart shadow in all cases was noted. In figure 2 is shown a case illustrating the successive changes in a patient with congestive failure and auricular fibrillation. Digitalis and Lugol's solution were given which, along with bed rest, cleared up congestive failure. (Normal rhythm was restored after operation and the heart shadow was further reduced in size.)

Congestive failure, in addition to auricular fibrillation, is undoubtedly partly responsible for the apparent

dilatation. Any treatment which clears up congestive heart failure, therefore, will probably produce a reduction in the size of the heart shadow. In some cases, Lugol's solution and bed rest will accomplish this result, but in others, in spite of this treatment, edema will increase, as we have frequently observed. Digitalis given at this point may produce marked diuresis. On the other hand, some cases with auricular fibrillation will show a reduction in ventricular rate following the use of digitalis but will not have diuresis until Lugol's solution is administered.

CHANGES IN THE SHAPE OF THE HEART

Attention has been called to the prominence of the pulmonary artery and other variations of the heart in toxic goiter.^{2,3,4,5} More recently Parkinson and Cookson² described the heart in this condition as ham-shaped. They state that this type of cardiac contour is due to a combination of prominence of the pulmonary arc, the left ventricle, and, to a minor extent, the right auricle.

The Pulmonary Arc. In this series we found the pulmonary arc to be prominent (i.e., straight or convex) in 52 cases on first observation. In 19 of

these we felt there was a definite reduction in size of the arc after operation or after clearance of heart failure. Prominence of the pulmonary arc was observed in some patients without auricular fibrillation or congestive failure; but the reduction in its size was

most marked in patients with congestive heart failure.

Transverse Diameter of Heart. By measurement, the transverse diameter of the heart was increased after operation in 48 cases. The change in position of the diaphragm accounts for a



FIG. 2. Heart shadows in a woman, aged 38, with exophthalmic goiter of 24 months' duration. Auricular fibrillation, mild congestive heart failure (positive Wassermann). Outline (1) before treatment. B.M.R. + 69, pulse 104, weight 109. Outline (2) after digitalis and Lugol's solution. B.M.R. + 40, pulse 90, weight 102. Outline (3) 18 months later. Normal rhythm present. B.M. R. (?), pulse 88, weight 123. Note generalized reduction of heart shadow after clearance of congestive failure and then further reduction of right border after restoration of normal rhythm.

large number of these increases. The right and left borders participated in this increase, but the left border accounted for the greater part, being influenced more by the position of the diaphragm. Superimposed films revealed that the ventricles, as well as the auricles, took part in the apparent dilatation. When decrease in the transverse measurements took place, the left border receded more frequently than the right border, although the latter often showed relatively large recessions, particularly after disappearance of congestive heart failure and cessation of auricular fibrillation.

Measurements of the Great Vessels and Base. The position of the great vessels in the chest underwent little change except in some instances of congestive heart failure where they appeared to be pushed upward. The measured width of the great vessels, however, showed changes. Reduction in this measurement was frequently seen in failure cases and probably most commonly was due to a decrease in the size of the pulmonary arc, which is included in the measurement. In a few instances a decrease in the measurement to the right was noted, which was probably accounted for by displacement of the aorta. Displacement of the aortic knob to the left may be due to intrathoracic goiter. Removal of the goiter allows it to return to its normal position. Increase in measurements of the great vessels after operation were seen in a few cases where there was an increase in blood pressure.

The measurements of the base were usually reduced in the cases which had had congestive heart failure, although this was by no means constant. The

difficulty in making this measurement in some cases renders it, in our opinion, of little value for comparative studies. The length of the heart appeared to be greater in cases associated with hypertension or other heart disease. In some cases the length of the heart showed a distinct reduction in the second film, especially, as in the case of the other measurements, after congestive failure had subsided.

Thus all measurements of the heart seem to be affected by the altered shape of the heart in congestive heart failure.

Other Changes Noted. Prominence of the superior vena cava was very infrequently noted. In one or two cases with mitral stenosis, the shadow of the vena cava was easily distinguished. Increased hilus markings were noted in many cases but more commonly in the failure cases. Diminution in the intensity of these markings after relief of failure or after operation occurred frequently. In cases with congestive failure, as a rule, the diaphragms were elevated. At times this seemed to be offset by the usual drop of the diaphragm from loss of weight so that very little change in position was noted in successive films. The cause of this elevation has been ascribed to enlargement of the liver. However, pulmonary congestion tends to render the lung tissue less elastic by virtue of the engorgement of the alveolar capillaries. In this way diminished vital capacity is brought about. Secondary atelectasis may occur. Thus it is reasonable to assume that the higher position of the diaphragm can be accounted for by these factors as well as by liver engorgement.

DISCUSSIONS OF FACTORS INFLUENCING THE SHAPE OF THE HEART IN HYPERTHYROIDISM

The cause of the prominence of the pulmonary artery in toxic goiter is unknown. There seems to be little doubt that it occurs, though the frequency of a straight or convex arc is rather high in patients without hyperthyroidism. In a consecutive series of teleoroentgenograms on 100 toxic goiter cases, 100 non-toxic goiter cases, and 100 non-goitrous individuals of approximately the same age and sex distribution, we found a straight or convex pulmonary artery region in 43, 30, and 32 per cent respectively. The most prominent arcs, however, appeared in the toxic goiter cases. Postmortem measurements made by Parkinson and Cookson² in six cases showed a 17 per cent increase in circumference of the pulmonary artery compared to normal standards. This should be confirmed by a larger series. This prominence must therefore be due to dilatation of the pulmonary artery presumably from increased pressure in this vessel.

Since enlargement of the pulmonary arc occurs without evidence of congestive heart failure, the origin of the increased pressure must be between the right ventricle and the pulmonary arterioles. Hyperthyroidism is characterized by a decreased peripheral arteriolar resistance but whether this drop also occurs in the pulmonary circuit is unknown. A vasomotor mechanism in the smaller vessels of the lung probably exists,⁶ but it is doubtful if the vascular bed in the pulmonary circuit would permit of vaso-dilation to such a magnitude as occurs peripherally. If this assumption

is true, then, with the increased output of the heart, the right ventricle would be working against a constant pressure in the pulmonary circuit. This inequality in pressures might soon lead to a gradually increasing intra-pulmonary arterial pressure and eventually dilatation of the pulmonary artery itself. In other types of heart disease increase in pulmonary pressure probably has its origin in the left ventricle and is transmitted backward to the pulmonary circuit or, as in mitral stenosis, it still begins in the left side of the heart but at the mitral valve. Thus in one, pulmonary pressure is elevated first at the pulmonary arterioles and transmitted back to the right side of the heart, and in the other the pressure begins at the arterioles of the systemic circulation, in the left heart or at the mitral valve and is transmitted back through the pulmonary veins to the pulmonary capillaries. Increase in pulmonary vein pressure may give rise to hemoptysis, paroxysmal dyspnea, and marked orthopnea. Increase in pulmonary artery pressure, as long as secondary effects do not take place, should not give rise to these manifestations. This seems to be borne out by clinical experience. Gallop rhythm is frequently seen in very toxic patients with hyperthyroidism and regular rhythm. Perhaps here too the relative inequality of pressure might play a part.

That the right ventricle becomes hypertrophied as well as the left is shown by postmortem examinations.² When gross left ventricular hypertrophy is seen in roentgenograms as indicated particularly by the blunt appearance of the ventricular shadow, hypertension is usually present and the

pulmonary arc is often less conspicuous. Enlarged auricular shadows contribute to the configuration of the heart in toxic goiter, the right probably more often than the left. When auricular fibrillation and congestive heart failure are present, dilatation of the auricles substantially alters the shape of the heart.

The incidence of the so-called ham-shaped heart is not great in our series. There are several explanations for this: First, surgical treatment is in more favor in this country than elsewhere, consequently, cases are referred for surgical treatment early in the course of the disease. Second, hyperthyroidism is generally more easily recognized than formerly, with the result that a larger number of patients over fifty, in whom hyperthyroidism is more difficult to diagnose than in those of younger years, are detected. Naturally, the incidence of other cardiovascular disease is high in these cases, the presence of which influences the shape of the heart.

SUMMARY*

Roentgenograms were made before and after treatment in 115 cases of

**Editor's note:* An extensive tabular report of cases is not published because of limitation of space.

toxic goiter. Comparisons of films were made by measurement and by superimposition. *Definite reduction in size* was observed after relief of congestive heart failure, and after cessation of auricular fibrillation, and in a few without these complications. Factors contributing to the shape of the heart in toxic goiter are enumerated and their probable causation discussed.

CONCLUSIONS

1. Superimposition of seven-foot roentgenograms of the heart is the most satisfactory method of judging changes in the size and shape of the heart.

2. Very little change takes place in the heart shadow in uncomplicated cases of toxic goiter with normal rhythm following removal of thyroid toxicity by subtotal thyroidectomy.

3. Cardiac dilatation as shown by roentgenograms takes place most frequently in congestive heart failure with or without auricular fibrillation.

4. Occasionally in cases of toxic goiter of sufficient duration, uncomplicated by other cardiovascular disease, certain changes in the heart shadow may be found which have been described as characteristic of hyperthyroidism.

REFERENCES

- ¹HURXTHAL, L. M., MENARD, O. J., and BOGAN, M. E.: The size of the heart in goiter, *Am. Jr. Med. Sci.*, 1932, clxxx, 772.
- ²PARKINSON, J., and COOKSON, H.: The size and shape of the heart in goiter, *Quart. Jr. Med.*, 1931, xxiv, 499.
- ³BAUER, J., and HELM, F.: Über Roentgenbefunde bei Kropfherzen, *Deutsch. Arch. f. klin. Med.*, 1913, cix, 73.
- ⁴KERR, W. J., and HENSEL, G. C.: Observations on the cardiovascular system in thyroid disease, *Arch. Int. Med.*, 1923, xxxi, 398.
- ⁵RÖSLER, H.: Das Röntgenbild des Herzens beim Hyperthyreoidismus, *Wien. Arch. f. im. Med.*, 1928, xv, 539-546.
- ⁶DALY, I. B.: Reactions of the pulmonary and bronchial blood vessels, *Physiol. Rev.*, 1933, xiii, 149.

Discussion of a Case of Gastric Carcinoma with Recurrent Colic*†

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NO reference is made in the literature to carcinoma of the stomach, producing attacks of pain resembling gall-stone colic. I wish to present such a case. The patient had attacks of typical gall-stone colic: sudden, severe pain in the right upper part of the abdomen under the costal margin, always requiring opiates for relief, and radiating always to the right shoulder region. Associated with this pain there were varying degrees of shock, manifested by pallor, rapid pulse, perspiration, weakness and prostration.

Pain is one of the common symptoms in cancer of the stomach. It varies considerably in its intensity, though the degree of distress is usually not excessive. In the early stages the patient may complain only of a sense of discomfort after meals, but as the condition progresses, actual pain manifests itself. There is nothing characteristic about the pain. It is usually of a dull, gnawing type; in some, it is of a burning character, and in others it may be sharp and lancinating. Cramp-like pains occur when there is associated pyloric

stenosis. In a few cases it may be so constant and severe as to be almost unbearable. Exceptionally, gastric carcinoma may occur with little or no pain. The pain may be intermittent or continuous. When intermittent it may occur only every few days or weeks. In not a few cases it is only nocturnal in its appearance.

A relation to food may or may not exist. Often foods increase the pain, especially if the cancer be pyloric, and in such instances, as in ulcer, it is usually relieved by vomiting. Or the pain may be continuous and bear no relation to the ingestion of food.

The site of the pain is usually in the epigastrium. It may, however, be complained of at the following sites: in the right upper quadrant, in the interscapular region, at the lower end of the sternum, low in the abdomen and at times in the left hypochondrium.

CASE HISTORY

S. P., age 58, peddler by occupation, reported to the Gastro-Enterologic Clinic at the Temple University Hospital on August 12, 1931. His past medical history was negative except for an attack of lobar pneumonia in 1917 and a double herniorrhaphy and appendectomy in 1919. He was perfectly well until one year ago when he had a nocturnal attack of sharp pain in the right upper quadrant, under the costal margin, which radiated to the back and the right shoulder area, and

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also across the abdomen to the left. The pain was of such intensity that a physician had to be called, and it was relieved only by the administration of a hypodermic of morphine. Since then he has had recurring attacks of similar pain, generally a few weeks apart, mostly diurnal and in each attack the pain was so intense that no relief was obtained until morphine was administered subcutaneously. There was no jaundice, chills or fever associated with the attacks, nor any urinary phenomena. The pain appeared without relation to food ingestion, or to physical exertion. His only worries were as to his health; he had no sorrows or griefs. There was no premonitory warning of an impending attack. An attack was never followed by any gastric disturbances such as nausea, vomiting or belching.

There was a loss of six pounds in weight in the past six months, and there was considerable loss in strength, so that for the last two months he felt he did not have sufficient stamina to carry on his work. His appetite lately was poor. There were no postprandial discomforts. The stools were light yellow to light brown in color and frequently contained mucus. There was never any blood in the stools.

Physical Examination. An adult Jew, of hyposthenic build, who appears to be about 60 years old. He is in no discomfort at the time of examination. Weight 125 pounds; height five feet, five inches. The pupils are equal and react normally to light and accommodation. The skin of the face is dry, weatherbeaten, and somewhat wrinkled. The tongue is clean, the teeth worn down and discolored, and the gums show food deposits. The tonsils are cryptic, the pharynx is congested, and there is a moderate cervical adenopathy. The thyroid is not palpable. The lungs are grossly negative; respiratory rate twenty. The heart is normal in size; the heart sounds weak; no murmurs present. The palpable arteries are slightly sclerotic. Blood pressure 140 millimeters of mercury systolic and 80 diastolic. Pulse rate 84.

The abdomen is scaphoid. There are two inguinal scars of a former herniorrhaphy. There is a tenderness in the epigastrium and over the gall-bladder region. There is no increased muscular tension anywhere nor is

any mass palpable. The liver edge is felt one centimeter below the costal margin. The spleen and kidneys are not palpable. The sigmoid is spastic. The rectal examination is negative except for external hemorrhoids. The knee jerks respond normally. Romberg test normal. Coördination normal. Babinski test negative.

The tentative diagnosis was cholelithiasis.

The routine studies made were as follows:—

Gastric. Fractional gastric analysis yielded a pearly-grey fasting residuum of ten cubic centimeters. There was no gross food retention, blood or pus present. Microscopically no Boas-Oppler bacilli or yeast cells were found, and there was no microscopic evidence of food retention.

The acid determination, employing an Ewald meal stimulus and one-half hourly extractions, was as follows:

	F	1	2	3	4
Free	0	0	22	22	32
Total	28	36	54	54	50
Bile	Pos.	Pos.	Pos.	Pos.	Pos.
Occult	Pos.	Pos.	Pos.	Pos.	Pos.
Blood	#1	#1	#1	#1	#1

As is seen, bile was present in the fasting and digesting stomach. The patient had taken the tube without gagging. According to Lyon¹ this is an abnormal finding and points either to disturbed physiology of, or to pathologic lesions within, the pyloro-duodeno-biliary apparatus. There are two exceptions to this: first, if the patient does not take the tube well but gags and coughs, bile may be regurgitated into the stomach; second, in cases of marked hyperacidity, the alkaline duodenal contents mixed with bile may be regurgitated into the stomach in a physiologic effort to lower the excessive acid. This latter mechanism is questioned by some observers.

We often find it difficult properly to evaluate the presence of occult blood. It is an abnormal finding if good tube technic is carried out. In office practice

where our technicians are properly trained and there is no hurry, the presence of occult blood is of considerable significance, and implies to us that we are dealing either with congestion, or erosion, or ulceration of the mucous membrane. But in clinic work, because of the large number of patients and the need for attention to as many as possible, tube technic is unfortunately not carried out with the same necessary care. We frequently find our technicians employing unnecessarily strong syringe suction in an attempt to extract a fraction hurriedly. Unless the benzidin reaction be very strong and the guaiac test positive, we attach no importance to occult blood reactions in the clinic. We grade our occult blood reactions plus one, two, three, and four. In plus one reactions we always think of trauma. In addition to trauma as a factor, we must also rule out mouth suction on the part of the patient. A good plan is to have the patient produce suction on his gums and then expectorate the material into a clean dish and test it for occult blood. The latter may also occur as a result of cricopharyngeus muscle spasm in the vagotonic type of individual. Physiologically, the two points of tonus in the esophagus, according to Jackson, are at the crico-pharyngeal orifice and at the hiatus. Vagotonics with excessive muscle strain can, during gagging, readily produce trauma at this upper point, and they often complain that they are sore, pointing over the cricoid cartilage, for some period of time after having had intubation of the stomach or duodenum. Even when the occult blood reaction is marked we must still keep in mind the possibility that we

may be dealing with a friable gastric mucous membrane. There is also the possibility that the presence of occult blood in any one fraction of the digesting stomach may be due to an abnormal amount of peristaltic contraction against the tip of the tube with consequent mucous membrane erosion.

We do not examine the gastric contents routinely for lactic acid because it is our opinion that it is not diagnostic of carcinoma. We do not agree with MacLean² who emphasizes the great value of its presence and who claims that it occurs frequently in large amounts at a very early stage in carcinoma. It is our conviction that lactic acid indicates only that stagnation has occurred and that gastric acidity is disappearing, and that it may accordingly be present not only in certain forms of gastric carcinoma but also in the benign pyloric stenoses when these cause a marked degree of obstruction, and may indeed be found in cases of marked motor insufficiency. This agrees with the findings of Murray and Robertson³ who reported that an investigation of test meals from 50 subjects, pathologic and normal, showed the presence of lactic acid in 74 per cent; it occurred more frequently in hyposecretion but was found present even in hypersecretion. Their conclusion was that lactic acid had no apparent clinical significance.

The Ewald meal was completely evacuated at about the two hour point, which indicates that gastric motility was normal. The final lavage revealed no food sediment remaining.

Biliary. A number of biliary drainages failed to show any cholesterol crystals or calcium bilirubinate pigment to be present.

The B fractions were of normal brown

color, and microscopy of all fractions failed to show evidence of any inflammatory involvement of the biliary system.

Bockus et al¹ have demonstrated that the finding of cholesterin crystals or calcium bilirubinate in the same bile is pathognomonic of gall-stones; and that the diagnoses of gall-stones based on the finding of cholesterin crystals without the characteristic pigment are 89 per cent accurate, and those based on bilirubin calcium pigment are 90 per cent accurate. It has been our experience that if in a number of successful drainages, i.e., those yielding good B fractions, we have failed to recover one of these two elements, especially in a centrifugated specimen, we may feel safe in saying that stone, in all probability, does not exist in the gall tract.

Urinalysis. Negative, except for trace of albumin. No pus cells or red blood cells were noted on a number of examinations.

Stool Study. The stools were of average size, light yellow in color, and of the usual fecal odor. There was no blood, gross or occult; no mucus, pus, nor grossly recognizable undigested food elements were present. Microscopy showed no free fat or undigested muscle fibers, indicating no failure of the external pancreatic or intestinal functions.

Blood Count. Hemoglobin, 85 per cent; red blood cells, 4,350,000; white blood cells, 7950. Differential white count, normal.

Van den Bergh Reaction. Direct, negative; Indirect, 0.2 unit.

Icterus Index. Six.

Liver Function Studies. Bromsulphalein: 2 milligram dose showed no retention at the end of 30 minutes. Galactose Tolerance, 3.3 grams. Urobilinogen, 1:5; Wallace and Diamond method, in which readings up to 1:10 are considered normal.

Blood Chemistry. Urea N 12 milligrams per 100 cubic centimeters; sugar 120 milligrams per 100 cubic centimeters.

Wassermann. Blood Wassermann and Kahn tests, negative. Spinal fluid Wassermann negative.

Blood Sedimentation. Normal horizontal line (Cutler graph).

The blood sedimentation test⁵ is a laboratory procedure which seems to have found a place as a valuable aid in diagnosis. When positive, it is an early indication of the presence of a destructive process as well as a measure of the intensity of the disturbance. Essentially the sedimentation phenomenon depends upon the amount of cellular destruction going on in the body. In healthy persons, as a result of the wear and tear of everyday life, a certain amount of tissue destruction is always taking place, and although this varies daily it remains within limits considered normal. Should, however, the amount of tissue destruction pass beyond the normal, then the stability of the blood is seriously disturbed and the red blood cells settle out quickly from the plasma. The rapidity of the settling of the red blood cells is in direct proportion to the severity of the underlying destructive process.

Roentgenologic Study (Dr. Chamberlain). No abnormality of the esophagus. The stomach is of average normal size, shape and position. Its outlines are smooth and regular throughout and its walls normally flexible. Gastric peristalsis begins soon after taking the barium meal and the stomach starts to empty in the normal manner. The outlines of the pylorus and the duodenum are likewise normal, but there is persistent tenderness in the right upper quadrant of the abdomen.

At six hours the stomach is empty and the barium is divided between the pelvic ileum and the cecum. The cecum is freely movable and not tender.

At 24 hours the distribution of the barium in the colon is normal and no abnormality of the large bowel is noted.

Films of the gall-bladder region, 13 hours after four grams of tetradol emulsion by

mouth, showed only a very faint gall-bladder shadow. To check up on this finding, the procedure was repeated on the following day. With the second examination we obtained 13 hour films which showed a gall-bladder of normal size and density, at the level of the disc between the second and third vertebrae. Films made two hours after a high fat meal showed the gall-bladder much smaller.

Conclusions. We have discovered no roentgen-ray evidence of organic disease in the gastrointestinal tract, and the findings in the gall-bladder suggest normal function.

*Gruskin Test for Malignancy.*⁶ Positive for carcinoma.

The Gruskin test is a flocculation reaction based upon the theory that, under normal conditions, epithelial and connective-tissue cells produce lysins that are antagonistic to each other and that due to their presence an equilibrium between these two types of cells is maintained. Because connective-tissue cells generate lysins which prevent the overgrowth of epithelial cells, carcinoma does not develop even though inciting factors (irritation, etc.) may be present. If, however, the connective-tissue fails to generate such lysins and the proper extrinsic factors are present, then carcinoma develops. The opposite condition holds true in the production of a sarcoma. That normal serum has the ability to autolyze cancer cells in vitro, whereas cancer serum fails to do so, has been demonstrated by Freund and Kaminer.⁷ In other words, in malignancy there is present in the blood stream a protein which is characteristic of the type of tumor, carcinoma or sarcoma, from which the patient is suffering, and this protein is typical for the type of embryonic cells of which the tumor mass is composed. When the serum of a patient suffering

with malignancy is brought in contact with an extract of embryonic cells of a homologous nature, flocculation takes place; when serum of a normal individual is thus tested, no such flocculation occurs.

Because of the positive Gruskin test and the normal sedimentation, we had to assume that malignancy, if present, was still in an early stage, that is, before tissue destruction had begun. A normal sedimentation rate is not conclusive evidence that there is no tissue destruction but it does show that disease, if present, is producing very little, if any, constitutional disturbance.

Because of the absence of positive findings, i.e., normal B fractions, negative bile microscopy and negative cholecystography, it was obvious, in spite of the fact that the symptoms were characteristic, that the diagnosis of cholelithiasis was probably not correct. There are a number of conditions that may produce attacks of pain resembling gall-stone colic. We therefore had to consider one of the following as a possible cause: cholecystitis; carcinoma of the gall-bladder; peptic ulcer, especially the perforating type; gastric crises of tabes; renal colic; appendicitis; pancreatitis; pancreatic calculus; lead colic; angina pectoris, and floating kidney. Weir and Partch have called attention to the fact that colicky attacks resembling gall-stone colic may also occur with cholangitis, cirrhosis and hepatitis, stricture of the common bile duct, and carcinoma of the pancreas.

Cholecystitis. Attacks of pain indistinguishable from gall-stone colic may occur in cholecystitis. The diagnosis is based on positive microscopic findings

of the biliary aspirates. The examination will reveal bile-stained, exfoliated, tall columnar epithelium often arranged in fan-shaped groups or rosettes; an excessive amount of mucus which may be encrusted with bile salts; an increased number of leukocytes proportionate to the extent of the inflammatory process; amorphous debris and occasional red blood cells. It must be remembered that negative findings do not necessarily indicate that there is no pathologic lesion, and in clinically suggestive cases if microscopy in the first study is negative the examination should be repeated.

Because of the absence of fever and leukocytosis, as well as the absence of positive microscopy over a number of drainages, and the presence of good function as demonstrated by cholecystography, the diagnosis of cholecystitis could not be supported.

Carcinoma of the Gall-Bladder. In the early stages, cancer of the gall-bladder often resembles cholelithiasis. In about 80 per cent of the cases gall-stones are found, and it is held by many that calculi are responsible for this condition. Because of the positive Gruskin test, this was a diagnostic possibility.

Peptic Ulcer. Gastric or duodenal ulcer, especially those with a tendency to perforation, may give rise to attacks of pain resembling gall-stone colic. Even with modern methods of study, mistakes in diagnosis between these two conditions are frequently made. As a rule the pain of ulcer has a direct relationship to food but so has the pain in certain cases of cholelithiasis, and in the latter the pain may be aggravated in some instances by dietary in-

discretions just as in ulcer. The pain of cholelithiasis in some cases may be present after every meal, and in cases of peptic ulcer there are usually well marked periods in which the patient is nearly or quite well. Hyperacidity speaks for ulcer, but according to Moynihan's statistics 22 per cent of his cholelithiasis cases showed hyperacidity, and in Rehfuß's experience more than one-half of his cases show hypersecretory findings. Though hematemesis and melena may occur in cholelithiasis it is an infrequent finding, whereas the presence of these symptoms speaks strongly in favor of ulcer.

The absence of such symptomatology in this case and the negative roentgen picture were against this as a diagnosis, although negative roentgen-ray findings do not exclude ulcer.

Gastric Crises of Tabes. The normal reflexes and the negative blood and spinal fluid Wassermann reactions excluded this condition as a possibility.

Renal Colic. The colic of nephrolithiasis is, as a rule, easily distinguished because of the radiation of the pain to the groin, the frequent micturition and the presence of blood, pus or albumin in the urine.

No stones were seen on flat plates. Urine examinations were persistently negative.

Appendicitis. Occasionally the cecum may be undescended, in which case the appendix lies close to the gall-bladder and an acute attack will be productive of pain simulating gall-stone colic.

The past history of appendectomy excluded this.

Pancreatitis. The pain in this condition is more directly in the epigastrium or to the left; there is a deep-seated

tenderness and resistance over the pancreatic area, and in an acute attack the shock and collapse is great and early in onset. Chronic pancreatitis may sometimes be detected by stool study; the movements are usually large, soft and pultaceous, and there is present free fat and undigested muscle fibers.

Normal stool findings over a number of studies, as well as the absence of such symptoms and physical findings as noted above, were against this condition being present.

Pancreatic Calculus. Colic may occur as the result of the passage of a calculus along one of the ducts of the gland. There is severe, deep-seated epigastric pain, generally associated with vomiting, glycosuria, steatorrhea and azotorrhea. The condition is rare and is usually mistaken for gall-stones.

The absence of the associated symptoms and signs did not favor such a diagnosis.

Lead Colic. Lead, by its stimulation of the motor nerves in the intestinal wall, causes violent spasm and contraction. The pain is felt about the umbilicus but often radiates from there into the right hypochondrium, suggesting biliary colic. The presence of anemia, a blue line in the gums, obstructive constipation, stippling of the red blood cells, tremor, palsies and an occupation involving exposure to lead suffice to make a clinical diagnosis.

The absence of the above symptoms exclude this from consideration.

Angina Pectoris. The pain of angina pectoris not infrequently may be referred to the epigastrium or to the right upper quadrant of the abdomen and may simulate an acute surgical abdomen. In such cases an acute coro-

nary occlusion is often the cause. In Heberden's angina pectoris the pain occurs or follows immediately upon effort; an attack may be induced by emotion and excitement, may follow upon exposure to cold, or may occur with gaseous distention after a heavy meal.

The patient was studied by the Cardiac Department and no cardiovascular lesion was found to be present. The electrocardiogram revealed no evidence of coronary disease.

Floating Kidney. That undue renal mobility, by producing traction on the duodenum and common bile duct or by kinking of the cystic duct, may induce attacks of biliary colic, has been pointed out by a number of observers. Marwedel⁸ states "a movable right kidney may produce all the symptoms of cholelithiasis—colic with or without jaundice—in the absence of diseases of the biliary passages". Moynihan⁹ refers to movable kidney as having caused confusion in diagnosis in some instances. Sherren¹⁰ has discussed this subject fully. He states "among thirteen cases in which symptoms suggestive of cholelithiasis were associated with movable kidney all except one were women. Gall-stones were present in two cases only. In none had urinary symptoms occurred. With regard to differential diagnosis this is difficult; even when the symptoms are due to movable kidney alone, tenderness will be present in the gall-bladder region during the attack, and Murphy's sign may be marked. When jaundice exists, the fact that the gall-bladder is distended should make us suspect that the movable kidney is the cause."

The attacks are almost always diurnal.

nal. The diagnosis depends on the detection of a floating kidney. The absence of a movable kidney in this case eliminated such a diagnosis.

Cholangitis, Cirrhosis and Hepatitis. The primary nature of cholangitis in some cases was pointed out by Judd and McIndoe.¹¹ This condition may progress to an obliterative process, giving the picture of stricture in the common bile duct with jaundice, or it may progress upward into the liver and lead to hepatitis or cirrhosis. Cholangitis may be the chief lesion in some cases; in others extensive hepatitis and cirrhosis is the predominant lesion. Weir and Partch¹² state that colicky pains occurred in more than 40 per cent of their cases. Jaundice often recurred repeatedly and chills, fever and sweats were not uncommon.

Negative biliary drainages, normal liver function tests, negative Van den Bergh reaction, and normal icterus index excluded the above as a possible cause.

Stricture of the Common Bile Duct. Most of the strictures occur postoperatively and follow upon cholecystectomy, choledochostomy, or both. In 50 per cent of the cases there is painless jaundice and in 40 per cent of the cases there is typical colic and jaundice.¹²

The absence of jaundice excluded this condition.

Carcinoma of the Pancreas. Pain is a common symptom and may or may not be associated with jaundice. If the head of the pancreas is involved, jaundice usually occurs early, whereas if the tail or body is primarily involved it occurs much later and pain is an early and more prominent symptom. Weir

and Partch report that colic typical of gall-stone occurred in five of their cases.

Because of the positive Gruskin test, carcinoma of the body or tail of the pancreas had to be considered.

A consideration of these facts led to the conclusion that we were probably dealing with carcinoma either of the gall-bladder or of the pancreas, and normal sedimentation rate and the absence of anemia suggested that the process was still in an early stage. We were cognizant of the fact that cancer of the gall-bladder, in about 80 per cent of the instances, occurs in association with gall-stones and the absence of stone tended to diminish the positiveness of such a diagnosis. Immediate operation was advised and the patient was admitted to the Babcock Surgical Ward. Operation was performed by Dr. Burnett September 24, 1931. His report follows:

The gall-bladder is whitish in color, only very slightly thickened, relaxed, and empties readily on pressure. No stones palpable. The cystic duct is not enlarged. The common duct is normal to palpation. The liver shows slight fibrosis and its edge is very slightly thickened. *Stomach:* The omentum is plastered over the lesser curvature. Underlying this area is a large mass saddling the lesser curvature; straightened out, the mass is about 10 by 4 centimeters. It lies about four centimeters proximal to the pylorus and extends to within six centimeters of the cardia. The mass has everted edges and feels like a malignant growth. No nodules are present in the gastro-hepatic omentum. Reëxamination of the liver shows no metastatic deposits to be present. The pancreas feels normal to touch and there is no evidence of fibrosis or growth.

The operation consisted of a gastric resection. The duodenum was partially mobilized and then resected below the pylorus and the distal and closed with Pagenstecher suture,

inverted and the adjacent mesentery ligated over the stump which was dropped; the jejunum was brought up and, at a point about fifteen centimeters from the ligament of Treitz, was anastomosed to the remnant of the stomach after the latter had been amputated on a radical line about three centimeters below the esophageal junction on the lesser curvature.

PATHOLOGICAL REPORT

Gross Description. The specimen is a rectangular piece of tissue 12 by 10 by 1 centimeters, removed from the wall of the stomach. In the central area, the continuity of the mucosal surface is broken and replaced by an ulcerative lesion 8 by 6 centimeters. The lesion is irregular in outline; its borders extend 1.6 centimeters above the mucosal surface and are hardened and eburnated. The base of the lesion is pale gray, rough, dull and moist. The surrounding mucosal folds are pink, moist and glistening; these too are thickened and hypertrophied. The external surface is rough, moist and glistening. Remnants of the mesentery are attached.

Microscopic Description. The mucosa is very much thicker than normal. On the inner surface there is a hyaline, structureless, mucus-like substance. The tubules are long and somewhat branched. Many mononuclear leukocytes lie in the tunica propria and there are a number of large lymph-follicles lying just above the muscularis mucosa. One end of the section, representing the edge of the ulcer, possesses tubules that are much less regular and very much more deeply stained than their fellows at the opposite end. About them, the leukocytic infiltration is intense. Everywhere beneath the muscularis there are masses of large, irregular, deep-staining cells with large reticular nuclei and pale-staining nucleoli. By higher magnification, many mitotic figures may be seen and it is noted that the cells are arranged somewhat in the form of glands. The reproduction is very crude. This cellular process is found even in the serosa.

Diagnosis. Carcinoma of the stomach.

COMMENT

The presence of carcinoma of the stomach in this case was an unexpected

finding, because to our knowledge attacks of pain resembling gall-stone colic have never been ascribed to cancer of the stomach and because none of our methods of study pointed to any gastric involvement. It demonstrated that gastric cancer may exist at a stage where none of our usual methods of study may give even suggestive information. Balfour¹⁸ informs us that by actual study 50 per cent of all cancers of the stomach are absolutely hopeless when seen by physicians in the Mayo Clinic, and one-half of the remaining 50 per cent are explored surgically and found hopeless. This means that only 25 per cent of all cancers of the stomach are within the possible reach of our best methods of treatment. Of all the diagnostic methods at our command the positive Gruskin reaction was the only one that detected the fact that we were dealing with malignancy. It was only our previous experience with malignancy-positive Gruskin reactions that warranted us to regard such a report with respect. That a malignant growth was present, even though the stomach had not been suspected, indicated that in the Gruskin reaction we have a method for the diagnosis of cancer that merits our attention.

Such a case is of interest because it once more compels us to ask ourselves how we are to diagnose the early case of gastric carcinoma. All of our present methods of investigation evidently are of little value in the diagnosis of cancer of the stomach at its incipient stage. The gastric analysis at the very earliest stage of the condition will reveal nothing. There is a latent period between the beginning of the carcinoma and the onset of symptoms. Radical

extirpation of the mass, at this stage, will result in cure. Our problem is to diagnose our cases in this latent stage. When gastric carcinoma produces the symptoms which we are taught are characteristic of carcinoma, then the condition has reached the inoperable stage. Palpable tumor mass, achlorhydria, lactic acid, Oppler-Boas bacilli mean that extension has occurred; anemia and cachexia imply that there is toxemia. It is necessary to emphasize that the early lesion of gastric carcinoma can exist in the presence of apparently perfect health.

Of all the methods at our disposal at the present time roentgen-ray examination stands preëminent in the diagnosis of cancer of the stomach. A positive roentgen diagnosis, however, can be made only if there is a defect present producing an anatomic alteration in the gastric contour. Roentgen-ray examination is very likely to fail us in the early stage of gastric carcinoma before a well developed lesion has occurred. When a defect has occurred 96 per cent of the cases, we are told, can be diagnosed in skillful hands by roentgen-ray.

Gastric analysis is practically of no value in the early stage of the disease. At this phase in its evolution there has as yet occurred no reduction in the gastric secretory output and the figures for both the free and total acid values are within normal limits. There may even be a slight increase in acidity at this stage in an otherwise healthy stomach; this is due to the irritation of the growth or its toxins. There may also be high acid figures especially in prepyloric carcinomas in the early

stage and in the malignant forms of ulceration almost to the end.

When pus, muco-pus and blood are present in the gastric contents the lesion is already definitely established. Minute particles of tumor tissue may be found on lavage and are perhaps conclusive evidence, but this is a very uncommon finding in early cases.

The objection might be raised that stone in the common duct was not excluded. We are cognizant of the fact that common duct stone may occur without jaundice. Clute¹⁴ reports that 39 per cent of the cases of common duct stone observed at the Lahey Clinic gave no history of jaundice in their previous attacks of pain and were not jaundiced at the time of operation. Judd and Marshall,¹⁵ and Jordan and Weir¹⁶ found that 20 per cent and 13.2 per cent of their cases respectively did not show jaundice before operation or at any time in their past history. Because of these facts the common duct should be explored more frequently at operation. Clute states that it is now his practice to open and explore the common duct in every patient: if it is dilated and thickened, whether or not stones can be palpated and regardless of any history of jaundice; in all patients who have had attacks of jaundice with pain, whether or not the duct is enlarged; in all cases in which there is much thickening of the head of the pancreas. Because at operation the common duct was not enlarged or thickened, or the head of the pancreas fibrosed, because there was no past history of jaundice associated with pain and because of the repeatedly negative bile microscopy, it was felt that there

was no need, nor any justification in view of the amount of major surgery already performed, to open and explore the common bile duct in this case.

PROGRESS NOTES

It is now one year since the patient was operated upon and he has not had a single attack of colic since. If any cause, other than his gastric lesion, was responsible for his attacks of colic it is not unreasonable to assume that he should have had a return of his attacks during the past year. This, I feel, proves the association between his carcinomatous lesion and the recurring attacks of colic. The mechanism involved in the production of the colic, in this case, cannot be definitely accounted for. We still are not able to explain adequately the cause of pain in the gastrointestinal tract. A summary of our present knowledge of the pathways along which abdominal pain travels is given by Alvarez.¹⁷ He states: "It seems now to be established that all afferent fibers in the sympathetic nervous system are connected with the posterior root ganglia of the spinal cord and are therefore no different from sensory nerves elsewhere in the body; they simply happen to travel in the same sheaths with bundles of sympathetic fibers. Most of those fibers which leave the upper part of the abdomen reach the spinal cord by way of the splanchnic nerves from the sixth to the ninth. In some persons the splanchnic nerves are connected also with the fourth, fifth, tenth, eleventh and twelfth segments of the dorsal cord. Blocking of the splanchnic nerves causes anesthesia of the visceral peri-

toneum and of the organs in the upper part of the abdomen.

"The vagus nerves carry so few sensory fibers that they can be ignored whenever efforts are being made to relieve abdominal pain. That these fibers are unimportant is shown by the fact that peritonitis is usually painless in the case of patients who have suffered injury to the upper part of the spinal cord, and by the fact that operations in the upper part of the abdomen can be done painlessly under splanchnic blocking.

"There are still other paths by which pain might conceivably leave the abdomen. One is by way of the ganglionated sympathetic chain, and the other is by way of the aortic plexuses and thence through the rami communicantes to the spinal cord in the upper dorsal region. That these sensory connections cannot be very important is shown by the fact already mentioned that when the spinal cord is severed in the upper dorsal region, disease in the abdomen usually runs a painless course."

The patient made an uneventful recovery following his operation. On leaving the hospital October 30, 1931 he weighed 115 pounds. November 16, 1931: His only complaint is weakness. Weight 116 pounds. December 17, 1931: Still complains of weakness; no digestive complaints. *Gastric Analysis*—no free hydrochloric acid; total acid 2.5 at end of one hour. *Blood Counts*—hemoglobin, 72 per cent, red blood cells 3,550,000, white blood cells 8100. *Sedimentation Rate*—average normal curve. *Van den Bergh*, direct negative; indirect 2 milligrams. *Icterus Index* 6. *Liver Function*—bromsulphthalein (2 milligram dose) no retention at end of 30 minutes. *Galactose*—3.0 grams. *Gruskin Reaction*—only very faintly positive; not even a one plus. January 15, 1932: *Gruskin Reaction*—very faintly positive, slightly stronger than on December 17, 1931. Dr.

Gruskin thinks he may be starting on a recurrence of his carcinomatous lesion. March 20, 1932: *Gruskin Reaction*—positive reaction, plus one. May 16, 1932: *Gruskin Reaction*—positive, plus one. June 15, 1932: *Gruskin Reaction*—positive, plus two. *Blood Count*—hemoglobin, 74 per cent red blood cells 4,010,000, white blood cells 8450. *Sedimentation Rate*: almost horizontal line. Feels stronger, is able to be at work for a few hours daily. Weight 118 pounds. Appetite good. No digestive complaints. Fluoroscopic examination discloses no delay in the passage of the barium meal and consequently no recurrence with obstructive phenomena. August 3, 1932: *Gruskin Reaction*—plus two. Complaints of weakness. Appetite fair. Weight 117 pounds. September 21, 1932: Had two weeks vacation and feels stronger; complaint now is not of weakness but of fatigability on exertion. Appetite good. No digestive discomforts if he eats small meals. Weight 118 pounds. Gruskin reaction same.

The persistence of a positive Gruskin reaction in this case is in all probability due to lymph node involvement. The regional lymphatic structures are large factors in the treatment of gastric carcinoma. To quote Balfour¹³: "There are two facts of great importance regarding enlarged lymph nodes in cancer of the stomach: (1) enlargement does not necessarily mean involvement by cancer, and (2) a patient may be cured even if all involved lymph nodes are not removed. The first fact is well known and undisputed and its practical importance is that it impels the surgeon to avoid the mistake of assuming

incurability because of marked and extensive enlargement of regional nodes, a fact to which W. J. Mayo early drew attention. The second point is less easily substantiated, but sufficient examples are found in this series of cases of cured patients, in which the surgeon considered the resection only palliative because of incomplete removal of an involved chain of lymph nodes. I believe it to be a possibility that in cancer in any situation, removal of the primary growth and of the immediately adjacent lymphatic structures may bring about a permanent cure even if involved lymph nodes are left; the remaining nodes in such cases act as a sufficient barrier to further dissemination of the disease. It is, therefore, occasionally good practice to disregard involvement of lymph nodes if the primary growth can be removed, and to remove the adjacent lymphatic structures as completely as possible."

CONCLUSIONS

1. Our present methods of study are often inadequate for the diagnosis of carcinoma of the stomach in its incipient stage.
2. In the Gruskin reaction we have a test for the diagnosis of malignancy that merits our attention.
3. Carcinoma of the stomach may produce attacks of pain indistinguishable from those of cholelithiasis.

BIBLIOGRAPHY

- ¹LYON, B. B.: Non-surgical drainage of the gall tract, 1923, Lea and Febiger, Philadelphia, p. 257.
- ²MACLEAN, H.: Modern views on digestion and gastric diseases, 1925, Constable and Company, London, pp. 99-103.
- ³MURRAY, I., and ROBERTSON, A. B.: Significance and origin of lactic acid in gas-

- tric contents, Brit. Med. Jr., 1932, i, 607-609.
- ⁴BOCKUS, H. L., et al: Comparison of biliary drainage and cholecystography in gall-stone diagnosis, with especial reference to bile microscopy, Jr. Am. Med. Assoc., 1931, xcvi, 311-317.
- ⁵CUTLER, J. W.: Practical application of

- blood sedimentation test in general medicine; observations based upon approximately 5000 patients over a period of six years, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 643-657.
- ⁶GRUSKIN, B.: Serum test for diagnosis of cancer based on a new theory of etiology, *Am. Jr. Med. Sci.*, 1929, clxxvii, 476-487.
- ⁷FREUND, E., and KAMINER, G.: Über die Beziehungen zwischen Tumorzellen und Blutserum, *Biochem. Ztschr.*, 1910, xxvi, 312-324.
- ⁸MARWEDELL, G.: Wanderniere und Gallenstein, *Beit. z. klin. Chir.*, Band 34, 1902, 477-507.
- ⁹MOYNIHAN, B. G. A.: Gall-stones and their surgical treatment, 2nd Ed., 1905, W. B. Saunders and Company, Philadelphia, p. 179.
- ¹⁰SHERREN, J.: Diagnosis of gall-stones, *Lancet*, 1911, i, 870-872.
- ¹¹JUDD, E. S., and MCINDOE, A. H.: Cholangitis, Jr. *Michigan Med. Soc.*, 1930, xxix, 174-179.
- ¹²WEIR, J. F., and PARTCH, W. T.: The relationship of pain to jaundice, *ANN. INT. MED.*, 1931, iv, 1509-1520.
- ¹³BALFOUR, D. C.: Curability of cancer of the stomach, *Surg., Gynec., and Obst.*, 1932, liv, 312-316.
- ¹⁴CLUTE, H. M.: Common duct stones, Jr. *Am. Med. Assoc.*, 1930, xcv, 1568-1571.
- ¹⁵JUDD, E. S., and MARSHALL, J. M.: Gall-stones in the common bile duct, *Arch. Surg.*, 1931, xxiii, 175-181.
- ¹⁶JORDAN, F. M., and WEIR, J. F.: Stones in the common duct without jaundice, *Proc. Staff Meet., Mayo Clinic.*, 1930, v, 56.
- ¹⁷ALVAREZ, W. C.: Abdominal pain; paths over which it travels and ways in which these may be blocked, *Am. Jr. Surg.*, 1931, xiv, 385-394.

The Poet of Flanders Fields*†

Lieutenant Colonel John McCrae, Canadian Army Medical Corps

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THE soldier poet who wrote the most arresting poem of the World War was Canadian, born of Scottish ancestry. He was the second son of David McCrae and Janet Eckford who were married January 21, 1870. The older son Thomas McCrae also became a notable man, a professor of medicine, the relative by marriage of Sir William Osler with whom he collaborated in the production of an encyclopedic treatise on medicine well known to most practitioners.

John was born November 30, 1872. He began his education when scarcely three years of age by learning the Shorter Catechism. This learning of the Catechism in what might almost be termed infancy, was a sort of test applied by many Scottish families to determine if the child were capable of becoming a scholar. If he passed the test successfully he was marked for the university and one of the learned professions, divinity, medicine or the

law. It is said on no less authority than that of Sir Walter Scott that it was the ambition of every Scottish mother to have her son "wag his head in a pulpit", and failing that to become a physician or an advocate.

Having passed the Catechism test, and having no doubt learned from it at so early an age that "He should renounce the devil and all his works, the pomps and vanities of this wicked world", as that noble and earnest document recommends for us to do, he in due time went to the grammar school and the high school. In 1888 he entered the University of Toronto with a scholarship, and graduated from the Faculty of Arts in 1894 with the Bachelor of Science degree, his major being in biology. He graduated in medicine and surgery in 1898, a gold medallist, with a scholarship in physiology and pathology. He entered immediately upon his internship in Toronto General Hospital. He had spent the previous summer between his junior and senior year at the Garrett Children's Hospital in Mt. Airy, Maryland. In 1899 he went to Johns Hopkins Hospital as a resident physician and then to McGill University as an assistant in pathology and assistant pathologist to the Montreal General Hospital.

At this point, however, his work was

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†This is the fifth of a series of portraits of medical poets. Those which have previously appeared in the ANNALS OF INTERNAL MEDICINE are:

Joseph Rodman Drake—February, 1929.

Oliver Wendell Holmes—June, 1930.

Oliver Goldsmith—May, 1932.

Wm. Savage Pitts—January, 1933.



DR. MCCRAE AND BONNEAU

interrupted by the Boer War. In addition to medicine he had two other major interests, poetry and military life. His father had been a militia officer, and at fourteen years of age John had joined the Guelph Highland Cadets. Now as a lieutenant of Canadian Artillery and a section commander he went out to South Africa on the

Laurentian. Here is one of his first letters from the war:

Van Wyks Vlei
March 22, 1900

Here I am with my first command. Each place we strike is a little more God-forsaken than the last, and this place wins up to date. We marched last week from Victoria west to Carnovan, about eighty miles. We stayed there over Sunday, and on Monday my sec-

tion was detached with mounted infantry, I being the only artillery officer. We marched fifty-four miles in thirty-seven hours with stops; not very fast, but quite satisfactory. My horse is doing well, although very thin. Night before last on the road we halted, and I dismounted for a minute. When we started I pulled on the lines but no answer. The poor old chap was fast asleep in his tracks, and in about thirty seconds too.

This continuous marching is really hard work. The men at every halt just drop down in the road and sleep until they are kicked up again in ten minutes. They do it willingly too. I am commanding officer, adjutant, officer on duty, and all the rest since we left the main body. Talk about the Army in Flanders! You should hear this battalion. I always knew soldiers could swear, but you ought to hear these fellows. I am told the first contingent had got a name among the regulars.

Here is another note of war and of a commander whose name is a byword in the British Army.

We were inspected by Lord Roberts. The battery turned out very smart, and Lord Roberts complimented the Major on its appearance. He then inspected, and afterwards asked to have the officers called out. We were presented to him in turn; he spoke a few words to each of us, asking what our corps and service had been. He seemed surprised that we were all Field Artillery men, but probably the composition of the other Canadian units had to do with this. He asked a good many questions about the horses, the men, and particularly about the spirits of the men. Altogether he showed a very kind interest in the battery.

At nine took the Presbyterian parade to the lines, the first Presbyterian service since we left Canada. We had the right, The Gordons and the Royal Scots next. The music was excellent, led by the brass band of the Royal Scots, which played extremely well. All the singing was from the psalms and paraphrases: "Old Hundred" and "Duke Street" among them. It was very pleasant to hear the old reliables once more. "McCrae's Covenanters" some of the officers

called us; but I should not like to set our conduct up against the standard of those austere men.

A veteran of the South African War, and with the Queen's Medal with clasps, he returned to Montreal to resume his practice, his place as a promising young pathologist, his teaching, his military drill, and his poetry. He was appointed physician to the Alexandria General Hospital, assistant physician to the Royal Victoria Hospital and a lecturer at the University. Eventually he became a fellow of the Royal College of Physicians and built a solid reputation as both a pathologist and an internist. He published a number of papers and at the time the World War began was finishing the revision of Adami's great *Textbook of Pathology*.

As early as 1894 he had begun to publish poetry, when two short poems "The Shadow of the Cross" and "The Hope of My Heart" appeared in the *Varsity*. In 1895 "Unsolved" was contributed to *The Canadian Magazine*. From then on until his death, *The Spectator*, *University Magazine*, *The Canadian Magazine* or the *West Minister* published nearly every year some verse by him. His contributions were not many, scarcely one or two a year, all short, and all similar in form and character. The usual or most common verse form was one called by the student of prosody the rondeau, and McCrae studied and experimented with this form until he was letter perfect in its use as a vehicle of poetic expression. The themes of his poetry were death, duty, and regret for lost love and life. It is possible that he was influenced by Houseman whose "Shropshire Lad", "that wonderful burst of song" as someone has called it, had

appeared in 1896. The elegiac note, the lament for loss is particularly a prominent feature of both poets.

One of the best of the poems is "Quebec" published in the *University Magazine* in 1908 on the occasion of the Tercentenary of the City.

QUEBEC

1608 1908

Of old, like Helen, guerdon of the strong—

Like Helen fair, like Helen light of word,—

"The spoils unto the conquerors belong.

Who winneth me must win me by the sword".

Grown old, like Helen, once the jealous prize

The strong men battled for in savage hate,

Can she look forth with unregretful eyes,

Where sleep Montcalm and Wolfe beside her gate?

"The Oldest Drama" from the *University Magazine* of 1907, "Upon Watts' Picture 'Sic Transit'", *University Magazine* 1904, "Isandlwana", *University Magazine* 1910, represent some of the best of his poetic work during the years of busy professional life.

He was a member of the Pen and Pencil Club of Montreal, a group of young writers and artists. He was popular socially and went about to social gatherings. He went fishing on his vacation and he made a number of journeys to Europe and the United States. How a fine looking and successful young doctor, five feet eleven inches tall, weighing one hundred and eighty pounds, and a poet, in fact in every respect the most eligible of bachelors, contrived to remain a bachelor during these years is difficult to understand, but he managed to do so, and in fact never married.

When the World War began in 1914 McCrae was in England but he at once

returned to become Brigade Surgeon to the First Artillery Brigade. Nearly his whole service before the World War, including the South Africa War, had been as a combat officer of artillery and he never quite got over a desire to continue as a line officer. He had plenty of war, however, as a medical officer, as these notes from two of his letters indicate:

Sunday, April 25, 1915.

On the front field one can see the dead lying here and there, and in places where an assault has been they lie very thick on the front slopes of the German trenches. Our telephone wagon team hit by a shell; two horses killed and another wounded. I did what I could for the wounded one, and he subsequently got well. This night, beginning after dark, we got a terrible shelling, which kept up till two or three in the morning. Finally I got to sleep, though it was still going on. We must have got a couple of hundred rounds, in single or pairs. Every one burst over us, would light up the dugout, and every hit in front would shake the ground and bring down small bits of earth on us, or else the earth thrown into the air by the explosion would come spattering down on our roof, and into the front of the dugout. Col. Morrison tried the mess house, but the shelling was too heavy and he and the adjutant joined Cosgrave and me, and we four spent an anxious night there in the dark. One officer was on watch "On the bridge" (as we called the trench at the top of the ridge) with the telephones.

Thursday, May 27, 1915.

Day cloudy and chilly. We wore our greatcoats most of the afternoon, and looked for bits of sunlight to get warm. About two o'clock the heavy guns gave us a regular "blacksmithing". Every time we fired we drew a perfect hornet's nest about our heads. While attending to a casualty, a shell broke through both sides of the trench, front and back, about twelve feet away. The zigzag of the trench was between it and us, and we escaped. From my bunk the moon looks

down at me, and the wind whistles along the trench like a corridor. As the trenches run in all directions they catch the wind however it blows, so one is always sure of a good draught. We have not had our clothes off since last Saturday, and there is no near prospect of getting them off.

Here is one with an observation by the poet doctor that was later to appear in "Flanders Fields":

and in the sky
The larks, still bravely singing, fly
Scarce heard amid the guns below.

Monday, April 26, 1915.

Another day of heavy actions, but last night much French and British artillery has come in, and the place is thick with Germans. There are many prematures (with so much firing) but the pieces are usually spread before they get to us. It is disquieting, however, I must say. *And all the time the birds sing in the trees over our heads.*

His horse's name was Bonfire and his dog's Bonneau. He wrote clever little notes as if from these animals, and signed those from the horse with a horseshoe as "Bonfire His Mark". References to animals and to trees and flowers are frequent in his letters and show his great interest in them.

"In Flanders Fields" appeared in *Punch* in the spring of 1915. Major General E. W. B. Morrison, who was in command of the brigade in which Major McCrae was serving, has in a letter described so well the actual circumstances under which the poem was written that his description is reproduced here:

"This poem", General Morrison writes, "was literally born of fire and blood during the hottest phase of the second battle of Ypres. My headquarters were in a trench on the top of the bank of the Ypres Canal, and John had his dressing station in a hole dug

in front of the bank. During periods in the battle men who were shot actually rolled down the bank into his dressing station. Along from us a few hundred yards were the headquarters of a regiment, and many times during the sixteen days of battle, he and I watched them burying the dead whenever there was a lull. Thus the crosses, row on row, grew into a good-sized cemetery. Just as he describes. We often heard in the mornings the larks singing high in the air, between the crash of the shell and the reports of the guns in the battery just beside us. I have a letter from him in which he mentions having written the poem to pass away the time between the arrival of batches of wounded, and partly as an experiment with several varieties of poetic meter. I have a sketch of the scene, taken at the time, including his dressing station; and during our operations at Passchendaele last November, I found time to make a sketch of the scene of the crosses, row on row, from which he derived his inspiration."

Here is the poem:

IN FLANDERS FIELDS

In Flanders fields the poppies blow
Between the crosses, row on row,
That mark our place; and in the sky
The larks, still bravely singing, fly
Scarce heard amid the guns below.

We are the Dead. Short days ago
We lived, felt dawn, saw sunset glow,
Loved and were loved, and now we lie
In Flanders fields.

Take up our quarrel with the foe;
To you from failing hands we throw
The torch; be yours to hold it high.
If ye break faith with us who die
We shall not sleep, though poppies grow
In Flanders Fields.

In the early summer after the sec-

ond battle of Ypres, the poet, now made famous overnight, was detached from the First Artillery Brigade and ordered for duty as Chief of the Medical Service at No. 3 General Hospital at Boulogne. At about this time also he was recommended for promotion to Lieutenant Colonel. He had many regrets at leaving the guns, but his services as an internist were of much greater value, and every medical man with specialist training was needed in the hospital now filled with sick and wounded after the desperate winter of 1915. He remained as Chief of Medicine until 1918 when he was selected to command General Hospital No. 1, but before he could assume this command it was proposed that he should be appointed "Consultant Physician to the British Army in the Field". He was never to receive either appointment. He contracted pneumonia and died at General Hospital No. 14 after an illness of only five days.

Each great war has furnished the inspiration for some great poem. There is little doubt but that "In Flanders Fields" is the poem of the World War that will linger longest in the minds of men. Its title, its simplicity, its easy measure, and its combination of elegy and call to duty are reasons for its sudden and wide publicity. With a music hall song, "It's a Long Long Way to Tipperary", it shares the honor of expressing best in fewest words the World War atmosphere and mood.

McCrae's scientific papers are well written, and his editing of Adami's Pathology well done. But there is one

short piece of prose that is more than well written and constitutes a fitting tribute to himself as well as being worthy to be considered beside the three other great tributes to the medical profession, namely the self-imposed Oath of Hippocrates with its lofty ethics, the well known eulogy by Robert Louis Stevenson, and Sir William Osler's address in which he refers to medicine as "a calling not a trade". Compare these with John McCrae on the legend from Watts' picture "Sic Transit", the subject of one of his earlier poems, and it stands the test well. Here is what he says of this profession: "What I spent I had: What I saved I lost: What I gave I have." "It will be in your power every day to store up for yourselves treasures that will come back to you in the consciousness of duty well done, of kind acts performed, things that having given away freely you yet possess. It has often seemed to me that when in the Judgment those surprised faces look up and say, 'Lord, when saw we Thee anhungered and fed Thee; or thirsty and gave Thee drink; a stranger, and took Thee in; naked and clothed Thee'; and there meets them that warrant-royal of all charity, 'Inasmuch as ye did it unto one of the least of these, ye have done it unto Me,' there will be amongst those awed ones many a practitioner of medicine."

BIBLIOGRAPHICAL NOTE

Most of the material for this article was obtained from Sir Andrew Macphail's tribute to Colonel McCrae, written in 1919, to accompany a collected edition of his poems.

Editorial

CERTAIN FACTORS IN THE LOCALIZATION OF DISEASE

The individuality of the various clinical forms of disease depends largely upon the tendency each exhibits to localize differently in the human tissues. The external specificity of symptoms and signs observed by the clinician corresponds to an internal specificity of pathological lesions or of functional disturbances. The factors entering into the determination of the specific localization of disease are to a large extent still obscure though from the earliest times they have been the subject of medical investigation.

In recent years there has been a renewal of activity in the study of the influence of heredity on the occurrence of disease. In addition to the well known hereditary anatomical anomalies it has been shown that certain of the heredo-familial degenerative diseases of the nervous system and certain metabolic disturbances such as pentosuria and alkaptonuria can be definitely followed as gene-determined characteristics. The list of such diseases is a large and important one. The lesions, especially in the diseases of the sense organs of the central nervous system, are as a rule exquisitely localized. Heredity is then an important factor which by as yet unknown mechanisms localizes disease of endogenous origin to specific sites in the tissues of the body.

Less definite in its findings has been the modern reinvestigation of the effects of constitution upon disposition to the various diseases. Borchardt defines constitution as the status of the organism as conditioned by both heredity and environment. It is the aggregate of those characteristics, anatomical, physiological, and psychical which constitute the total individual. Various types of constitution have been described such as the slender or asthenic type and the broad or pyknic type. These separate types of constitution have been shown to exhibit a difference in their disposition to many diseases such as tuberculosis, gout, diabetes, gall-stones, asthma, peptic ulcer, etc. In some instances these variations in disposition seem to be linked with variations in physiological functions which might be causative. For the most part, however, constitutional pathology does not offer explanations of its findings. It is in the descriptive rather than in the elucidative phase of its development. We may accept the fact that constitution to some extent determines the localization of disease in the body.

The study of these more general phenomena, heredity and constitution, has been accompanied in our day by an attack on the problem of disease localization carried on from quite a different angle. The investigations to which we refer have dealt with the more intimate mechanisms by which

local tissue immunity or susceptibility are determined. These studies have been concerned chiefly with the problems connected with the localization of the infectious diseases, and with the localized effects of toxins, drugs, and poisons.

The degree to which bacteria are invasive has long been conceded to be the result of a balance between two opposing factors: the "virulence" of the bacterial species and the resistance of the host.

Virulence is at best a vague, all-inclusive term used to cover the sum total of all the harmful effects of a bacterial species. Included in it is the power of a particular strain to attack successfully highly localized areas within the body of the host. To an increasing extent in recent years this specificity of effect of certain bacterial strains has won recognition and the bitter opposition which met Rosenow's pioneer work in this field has to some extent died away. The problem of bacteriology is now to determine in how far tissue specificity shown by pathogenic organisms is related to the specificity of the types into which the bacterial species *in vitro* can be subdivided. These types until recently could be considered specific only upon the basis of specific immunologic responses incited by their injection. The brilliant researches of Avery and his co-workers have given us evidence in the case of the pneumococcus, that type specificity and virulence are alike functions of the capsule of the organism, and that the capsule of each type of pneumococcus contains a polysaccharide which is chemically and immunologically distinct from that contained in the capsule of

the other types. Such light thrown upon the nature of type specificity within the bacterial species must serve in time to enlarge our understanding of the mechanism of tissue specificity of bacterial action in the body, with a consequent expansion of our knowledge of the factors in the localization of the bacterial diseases.

The relationship of the chemical constitution and physical state of a substance introduced into the body to the localization of this substance in the organs of the body was studied intensively by Ehrlich and led directly to his bold conception of union by chemical affinity between protoplasm and the injected drug or dye or toxin. He was led by this conception to search for specific drugs which would be toxic to parasites and possess a strong chemical affinity for them, while showing only a weak chemical affinity for the tissues of the host. Such a substance could be administered in sufficient dosage to kill the infecting organism and leave the host unscathed. The enunciation of the theory of chemotherapy has been enormously valuable because of the stimulation it gave to the synthesis of large series of new chemical compounds and to their trial as therapeutic agents. The attempt to explain their distribution and action on the basis of chemical affinities has met with difficulties which have somewhat blurred the simple outlines of the original theory. A further difficulty and disappointment of the chemotherapeutic era has been the repeated demonstration of the fact that the parasitidal action of a chemical substance *in vitro* very often does not correspond to its action on the parasite in the animal body. The orig-

inal compound introduced may be altered by oxidation, reduction, or synthesis in the body and it may be only the end product of such reactions that is available for chemotherapeutic action. It has been found also that the effectiveness of certain drugs seems to be as an adjuvant to the immune reactions of the host and that the optimum dose for this joint action lies well below the maximal dose which would be tolerated. Perhaps the essence of the difficulty in chemotherapeutic research lies in the fact that whereas the chemical constitution of the prepared remedy is known, the nature of the physicochemical medium in which it must act, and the chemical nature of the parasitic or host protoplasm with which it is intended to join, are both still obscure. A large measure of empiricism must prevail in chemotherapy while it still deals with such unknown factors. It may be that the separation of the chemical fractions of microorganisms, a line of investigation which in the hands of Heidelberger and others has revealed the chemical compounds responsible for the type characteristics of the pneumococci, will eventually simplify the task of chemotherapy by indicating the precise nature of the substance on which the chemical remedy must act. A sound theory of the nature of the affinity which localizes the action of a drug or a toxin must await further knowledge.

These investigations which are attempting to reduce to terms of chemical constitution and physical state the attributes of bacteria and of drugs which give specificity to their biological behavior have been supplemented by studies bearing upon the variations in

resistance of the various tissues and organs of the host.

It is apparent that the exterior of the body of the host offers in different areas a variable degree of resistance to invasion, the basis of which lies in structural differences. The toughness and impermeability of the skin as compared to the delicacy and absorptive power of the mucous membranes, the heat and moisture in the folds of axillae and groins as compared with the hands, the differing degrees of exposure to trauma and friction, all such structural and functional differences in the exterior of the body are no doubt important factors in determining the localization of the portals of entry of the infections.

When the infection is within the body, however, and in process of dissemination through the blood stream, the factors which determine its secondary localizations in certain sites while leaving other parts uninvolved offer fascinating problems. It is reasonable to suppose that once within the closed system of the circulation, bacteria, drugs, toxins, or other foreign material will pass out again into the tissues at the points where the vascular wall is most readily permeable. The capillary wall towards the venous end of the capillary has been shown to be the most permeable portion of the vascular system. The nature of this permeability, and its control by the autonomic system, by hormonal action, and by the physicochemical constitution of the blood and tissues, have been intensively studied in recent years. Burrows has recently summarized our present knowledge of how local changes in

capillary permeability may lead to localization of disease, and has cited a vast number of experimental and clinical observations which indicate the actual importance of this factor.

The advance of our knowledge of capillary permeability has depended largely upon two methods: The visualization of the capillaries and the use of injections of dyes which by the greater intensity of staining make manifest the area in which permeability has been increased. By a combination of these methods it has been shown that increased permeability of capillaries may be quite independent of dilatation and even of stasis. Local inflammation, local ischemia, local increase in hydrogen ion concentration, local disturbance of vascular innervation, local action of histamine-like substances, may be accompanied by a local increase in capillary permeability as shown by a localization of injected dyes. Moreover, it has been shown that the capillaries in such an area may remain more than normally permeable for some time after the inciting cause has disappeared. These experimental observations with dyes throw light on the mechanism involved in certain further experimental studies dealing with the localization of disease.

The tendency of blood-borne infections to localize in traumatized areas has been repeatedly proven by experimental methods and corresponds closely to similar localizations of injected dyes. The normal brain and spinal cord always remain free from dye injected intravenously, but Macklin and Macklin found that if rats were injected with trypan blue and then given blows on the head this trauma was sufficient

to localize the dye in the brain as shown by a pronounced staining of the tissues. Okuneff applied a hot water bag to the abdomen of a rabbit and then gave an intravenous injection of trypan blue. As a result not only was the belly wall where it had been in contact with the hot water bag strongly colored, but so also were the subjacent coils of intestine. Ebbecke has reported that if trypan blue or trypan red be injected into the general blood stream and a wheal be then produced in the skin, the dye will discolor the wheal. Similarly Chesney, Turner and Halley excised pieces of skin from the backs of rabbits and later gave intravenously 0.1 c.c. of a testicular emulsion of active treponemes. At periods varying from nineteen to sixty-seven days subsequent to these injections every one of the dorsal scars became affected with indurated syphilitic lesions, whereas no other cutaneous lesions occurred. In humans the tendency for secondary syphilitic eruptions to be more intense about old scars, chronic ulcers, and areas of irritation has been repeatedly noted. The tendency of the lesions to be most numerous about old tattooing is especially striking. Krause injected cultures of tubercle bacilli intravenously into rabbits and then wrenched a joint. In one-half of these rabbits the injured joints became tuberculous. In septicemia due to typhoid bacilli, pneumococci, or staphylococci, secondary localizations at sites of trauma, of pressure, or even of hypodermic injections have been very frequently reported. In the experimental studies of the virus diseases various forms of irritation as a means of localizing the disease have been repeatedly employed

by many investigators. The virus of vaccinia when intravenously given will produce a vaccinal eruption wherever the skin has been traumatized. Flexner and Amoss found that infection of the nervous system with poliomyelitis virus given intravenously could only be obtained if enormous doses were employed. If, however, an intraspinal injection of foreign serum had been made twelve or eighteen hours beforehand, infection was readily established by giving virus intravenously.

A mass of experimental work, from which these few illustrative examples are drawn, points strongly towards the dominant rôle of local variations in capillary permeability as a factor in the localization of blood-borne diseases.

Beyond the capillaries lie the extracellular tissue fluids and the tissue cells. It is not sufficient that a noxious agent permeate the capillary endothelium; it must also exert its effect upon the extravascular tissues before evidence of

a localized lesion appears. Gay has discussed the variable resistance of the tissues to such invasion. Theoretically, he points out, successful local resistance might be due to local formation of antibody, or to a local accumulation of antibody formed elsewhere. He sets aside both hypotheses, however, and inclines to believe that local resistance is not humoral but chiefly cellular in character. In this connection he has brought forward evidence that a particular type of macrophage, the clasmatocyte, plays the chief rôle in local defense reactions and he suggests that the varied susceptibility to infection of different tissues depends chiefly upon the distribution among them of this macrophage.

Necessarily in this brief review many aspects of the localization of disease have not been mentioned. Enough perhaps has been said to indicate some of the recent lines of attack upon this fundamental problem of human pathology.

Reviews

Intracranial Tumors. By PERCIVAL BAILEY, Professor of Surgery, University of Chicago. xx plus 475 pages, with 155 illustrations. Charles C. Thomas, Springfield, Illinois, 1933. Price, \$6.00.

This book comes at a very opportune time for students and those interested in the subject of intracranial tumors, because it is the first of its kind to present the whole subject from a much needed clinico-pathologic viewpoint. The material is presented in the readable style of informal clinics, which were amplified for publication. Fifty-nine illustrative cases from the author's clinic form the basis of the text.

The opening chapters include a discussion of the problem of tumors in general, the

modern classification of intracranial tumors, and valuable analytic tables. The more fundamental anatomic and physiologic conceptions are also reviewed. Each type of intracranial tumor is presented from the clinico-pathologic viewpoint, with emphasis on the latter. The author correctly stresses the view that it is no longer sufficient to know that a patient has a brain tumor and its location, but the histological type as well. Several clinical cases are given to illustrate each histological type. From case histories the clinical story of each individual type of tumor is developed. The general characteristics, the age incidence, the common location of the tumor, the gross appearance, and the microscopic anatomy are discussed. The his-

tory of the developing neoplasm is given by detailed review of symptoms and the resultant neurologic signs. Each tumor is described in the location in which it is most commonly found, with a discussion of the neurologic syndromes which result from neoplastic invasion of each cerebral subdivision. In the chapter on medulloblastoma, for instance, the syndrome of the vermis cerebelli is outlined; in connection with hypophyseal adenomas, acromegaly and the hypopituitary syndrome are discussed. Regional physiology and anatomy are included in the discussion of the neurologic signs and symptoms of each syndrome. A brief note concerning the accepted treatment is given for each tumor. Chapters on general diagnosis, differential diagnosis, and general treatment of intracranial tumors conclude the book.

The text is printed on dull paper and adequately illustrated with 155 pen-and-ink drawings. While reading is made easier by the use of dull paper, this is done at the expense of eliminating the usual and preferable half-tones. Photomicrographs would have added to the illustrations. The bibliography contains some four hundred references which serve as a valuable guide for supplementary reading. The book is exceptionally well done and deserves a place in the library of any one interested in intracranial tumors.

J. G. A., JR.

Diseases of the Heart. By SIR THOMAS LEWIS. 297 pages. The Macmillan Company, New York. 1933. Price, \$3.50.

This book is written in the author's usual clear and succinct style. It is purposely designed for use by practitioners and students, and will be of little value to one who is already primarily concerned in diseases of the heart. The subject is approached largely from the point of view of bedside observations, and these are clearly stated. The author has a particularly sane and common sense attitude toward the limitations of the usefulness of digitalis and toward the handling of patients suffering with essential hypertension. Many cardiologists would be more optimistic in regard to the usefulness of quinidine in the therapy of auricular fibrillation. There is perhaps too little discussion of the information to be obtained from

electrocardiography and other mechanical methods, and too great stress placed upon somewhat unreliable clinical methods. The reviewer certainly cannot agree with the following statement: "The fingers should be trained to recognize a high tension pulse; for a pressure meter can hardly be used as a routine in general practice." The discussion of those patients with complaints referred to the heart and who present no evidence of heart disease is inadequate. Such patients, both in their diagnostic and therapeutic implications offer serious problems for the practitioner. The author has dealt with them in a very short chapter on the "Effort Syndrome," and a paragraph or so on the occurrence of heart pain in neurasthenia, which latter term is apparently used as a sort of catch-all for neurotic invalidism. The reviewer sees little reason for not dealing with the "Effort Syndrome" in a chapter devoted to the psychoneuroses. However, because of its clarity and lack of extensive theoretical discussions, and because of the author's excellent clinical observations, and his conservative and common-sense approach to the whole subject, this should prove a valuable book for the general practitioner.

W. S. L., JR.

Outline of the Cranial Nerves. By JOHN FAVILL, A.B., M.D., F.A.C.P., Associate Clinical Professor of Neurology, Rush Medical College of the University of Chicago. Cloth. 120 pages. The University of Chicago Press, Chicago, Illinois. 1933.

This little book should be of decided value to the medical student or to any one interested in the study of Neurology. Each cranial nerve is treated under five headings: anatomy, function, tests, pathology and localization, thus bringing together facts that are usually not found under one classification. The chapter relating to the eighth nerve is especially good—giving a full account of the vestibular tests and their significance.

Considered as a whole, this is an excellent summary of our present day knowledge of the cranial nerves.

A. C. G.

Clinical Aspects of the Electrocardiogram. By HAROLD E. B. PARDEE, M.D. Third edition, revised. 295 pages. Paul B. Hoe-

ber, Inc., New York. 1933. Price, \$5.50.

The third edition of this book has been revised and somewhat amplified. The author has accepted the newer views in regard to the localization of premature ventricular beats and of the myocardial lesions giving rise to bundle branch block and has revised his terminology accordingly. The chapters on changes in the electrocardiogram due to myocardial disease, and the clinical significance of abnormal waves should be of general interest. The author happily points out that while certain of such changes undoubtedly mean temporary or permanent serious myocardial disease, and others probably indicate abnormalities of the myocardium, one is not justified in making a prognosis upon the electrocardiogram alone. One too often sees patients who have been frightened unjustifiably by a diagnosis of myocardial disease based upon slight deviations of uncertain meaning from the normal electrocardiogram. Ventricular axis deviation and the arrhythmias are adequately covered and there is a clear exposition of the theory of the electrocardiogram. The two types of electrocardiograph are described and the technic of their use explained. The book should be readily understood by the practitioner of medicine and should be of value also to those primarily interested in heart disease.

W. S. L., Jr.

Procedure Book of the Methodist Episcopal Hospital. 2nd Edition. Brooklyn, New York, 1932.

This small volume is a paper bound book of two hundred and one printed pages, containing twenty-five chapters and an index. Between each chapter there are six blank pages for additional notes. Its size, 6 x 9 inches, precludes the possibility of its being carried about in the pocket.

Originally prepared to serve the undergraduate nurses of the Methodist Episcopal Hospital, the book has been expanded in this edition to be of service also to the interne staff. All printed procedure books are of interest to the superintendents, heads of training schools, chiefs of services, and house officers of other hospitals. They contain much valuable information which can be taken over to serve in the construction of

new procedure books. This little volume is quite complete and contains a vast amount of useful data. One strange omission is the lack of any mention of blood transfusions. It is also of interest, though not important, that though the junior nurses are specifically forbidden to sing, whistle, or play musical instruments, no mention of the rules as to smoking is made.

M. J. A.

Diseases of the Eye. By HOFERAT ERNST FUCHS. Revised by MAXIMILIAN SALZMAN. Translated by E. V. L. BROWN. Tenth English Edition. 255 illustrations and 41 colored figures. J. B. Lippincott Company, Philadelphia. 1933. Price, \$7.00.

This volume, which constitutes the tenth English edition of Fuchs' famous *Textbook of Ophthalmology*, has been reduced approximately one-third in the number of pages as compared with recent editions. The lessened size is due largely to the elimination of Part I of the former work consisting of Chapter one (Objective Examination of the Eye) and Chapter two (Functional Testing), Part III which took up anomalies of Refraction and Accommodation, and Part IV which gave a concise description of the various operations upon the eye and its adnexae.

There has also been a considerable rearrangement of the subject matter. Part I treats of the Lids and Conjunctiva; Part II, Diseases of the Tunica Fibrosa (Cornea and Sclera); Part III, Diseases of the Uvea; Part IV, Diseases of the Retina and of the Optic Nerve; Part V, Diseases of the Lens, Zonule and Vitreous; Part VI, Diseases of the Eyeball as a Whole; Part VII, Diseases of the Orbit and Part VIII, Diseases of the Nerves of the Eye.

While the rearrangement of material may be an advantage and the elimination of Parts I, III, and IV may be gratifying to the undergraduate, these changes certainly will not be pleasing to the postgraduate student who has looked upon his Fuchs' as his Ophthalmic Bible.

It would seem that greater attention should have been directed to the use of the slit-lamp in determining microscopic changes in the living tissues, as an aid to diagnosis. The reviewer also believes that greater attention should have been given to the therapeutic use

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of tuberculin in the treatment of the various tuberculous lesions. The modern conception and treatment of retinal detachments could also be made more explicit.

In spite of the somewhat limited scope, the book is still a very valuable work upon the diseases of the eye.

C. A. C.

Criteria for the Classification and Diagnosis of Heart Disease. By The Criteria Committee of the Heart Association, New York Tuberculosis and Health Association, New York. 131 pages. 1932. One can only be in sympathy with the purpose of this publication. It should serve as an important step towards the adoption of a uniform nomenclature for heart disease, and uniform criteria for using such nomenclature. The book deals with etiological, anatomical and physiological diagnosis, and the functional state of the heart. In the appendix are sections on electrocardiography and radiography. It is not a clinical exposition of heart disease, but as an aid in classifying cases it should prove most valuable to any physician interested in internal medicine.

W. S. L., JR.

The Doctrine of the Healing Power of Nature Throughout the Course of Time. By MAX NEUBURGER, M.D., Ph.D., Professor of History of Medicine of the University of Vienna. Translated by LINN J. BOYD, M.D., F.A.C.P., Professor of Pharmacology, The New York Homeopathic Medical College and Flower Hospital. Paper. 184 pages. 1933.

To those interested in the history of medicine, particularly from its philosophical aspects, this monograph by one of the world's greatest medical historians should be of considerable interest. The doctrine of the healing power of nature has occupied the attention of the physician for thousands of years. Today, it is probably of greater importance than at any time in the past. Our studies of the internal secretions and of immunity have brought the matter to the forefront. Dr. Neuburger traces the history of this subject from the days of Hippocrates, when the occurrence of spontaneous healing was established as a fact for the first time, through the ages down to modern times.

Dr. Boyd's translation is excellent.

A. C. G.

College News Notes

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. W. R. Brooksher (Fellow), Fort Smith, Ark.—2 reprints;
Maj. Leon A. Fox (Fellow), Washington, D. C.—2 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—1 reprint.

Dr. Arthur L. Bloomfield (Fellow) has been appointed Acting Dean of Stanford University School of Medicine, San Francisco. Dr. Bloomfield is also Professor of Medicine and Secretary of the School.

Dr. John Severy Hibben (Associate), Pasadena, Calif., has been appointed Chairman of a Special Committee on Physical Therapy of the California State Medical Association to survey the present practice of physical therapy with reference to education and practice, and to report on it at the next meeting of the State Medical Association.

Dr. Walter L. Bierring (Fellow), Des Moines, Iowa, has been appointed State Health Commissioner for Iowa, beginning July 1.

Dr. Maxim Alexander Oginsky (Fellow), formerly Medical Director and Pathologist to the Saratoga Hospital at Saratoga Springs, N. Y., was appointed April 1, 1933, as Di-

rector of Laboratory and Pathologist to the Woman's Hospital, Detroit, Mich.

Dr. James A. Lyon (Fellow), Washington, D. C., and Dr. Lewis C. Ecker (Associate), Washington, D. C., are President and Vice-President, respectively, of the Washington Heart Association.

Dr. Lawrason Brown (Fellow), Saranac Lake, N. Y., was recently reelected President of the Saranac Lake Society for the Control of Tuberculosis.

Dr. William S. Rude (Fellow), Ridgetop, Tenn., was recently elected one of the Vice-Presidents of the Tennessee State Medical Association.

OBITUARIES

DR. MARTIN JAMES LARKIN

Dr. Martin James Larkin (Fellow), Toledo, Ohio, died March 11, 1933; aged 39 years. On the evening of July 9, 1932, while on his way to the Mercy Hospital, he was apprehended by a man who demanded his car. While he was in the act of leaving his car, the gunman opened fire on him. The bullet entered the left side of the face, fractured the mandible, passed through his mouth and lodged in the neck, opposite the transverse processes of the second and third cervical vertebrae. Dr. Larkin recovered from the wound; the fractured mandible united and he apparently returned to normal, so that he returned to practice on January 3, 1933. On January 18, he complained of pain in the cervical region. Two days later an abscess was evacuated, and one week later the bullet was removed. Several days later he gave signs of cerebral irritation and of bloodstream infection. His condition became progressively worse, and he expired on March 11, 1933.

Dr. Larkin was a graduate of St. John's University, Toledo, receiving the degree of A.B. in 1915. He received his medical education at St. Louis University School of Medicine, graduating in 1919. For two years

thereafter, he served on rotating services of the St. Louis City Hospital, and then entered general practice in Toledo. His work had been devoted chiefly to Internal Medicine and Tuberculosis since 1924. His appointments included Director of the Department of Medicine, Mercy Hospital; Assistant Director of the Department of Medicine, Lucas County Hospital. He was a member of the Toledo and Lucas County Academy of Medicine, the Ohio State Medical Association and the American Medical Association. He became a Fellow of the American College of Physicians on March 22, 1931.

DR. EDWARD W. MEIS

Dr. Edward W. Meis (Fellow), Sioux City, Iowa, died December 7, 1932, of carcinoma of the stomach.

Dr. Meis received his medical degree from the University of Iowa College of Medicine in 1900. At the time of his death, he was Senior Examiner for the Prudential and Missouri State Life Insurance Companies; a member of the Sioux City Chest Clinic; a member of the staff of St. Joseph's Mercy Hospital.

He was a member of the Woodbury County Medical Society, the Iowa State Medical Association and the

American Medical Association. He became a Fellow of the American College of Physicians on February 24, 1920, and had served actively throughout his entire membership.

DR. FRANKLIN E. MURPHY

Dr. Franklin E. Murphy (Fellow), Kansas City, Mo., died, February 20, 1933, of heart disease; aged, 67 years.

Dr. Murphy was born November 21, 1866, at Reddington, Ind., the son of a physician. His family moved successively from Reddington to Independence, Mo., and then to Kansas City, where he received his secondary school training in the Central High School. Dr. Murphy continued his studies at the Philadelphia College of Pharmacy, graduating in 1888. After acting as a pharmacist for one year, he entered the University of Pennsylvania School of Medicine, from which he graduated in 1893. From 1896 to 1901, he was Secretary of the Kansas City Medical College; from 1901 to 1903, he pursued postgraduate work in the Universities of Göttingen, Jena, Berlin and Vienna. Shortly after his return to this country, he became Professor of Clinical Medicine in the University of Kansas School of Medicine, serving in this capacity from 1905 to 1933.

Dr. Murphy was President of the Jackson County (Mo.) Medical Society, a member of the Missouri State

Medical Association and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1920. He was a member of the Staffs of the Bell Memorial, Research, Wesley and General Hospitals.

"His record shows the career of a man who chose his profession with a full knowledge of its difficulties and trials, and steadily pursued his course of primary, professional and postgraduate instruction. This is evidence of his determination of character, as he had to earn his own way. His professional ability was recognized by members of the profession, and he was appointed to responsible positions as a teacher of medicine and elected to executive responsibilities in medical organizations."

". . . Franklin E. Murphy was a man of positive character. No one, friend or enemy, was ever heard to speak of him except in terms of respect. He always took his work seriously and was a hard, patient and methodical worker. His patients all respected him and those with whom he came in intimate contact loved him." Dr. Murphy was a man who could always be relied upon to support the best traditions of the profession.

(Furnished by A. COMINGO GRIFFITH, M.D., F.A.C.P., Governor for Missouri.)

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